Welcome to Vancouver and the 32nd Annual Meeting of the Society for Clinical Trials! I especially welcome those who might be attending our meeting for the first time. We are all in for a treat!

The SCT officers and Board of Directors are excited about this year’s meeting and are confident you will find the wide range of current clinical trial topics to be presented both informative and enjoyable. As always, our sessions attempt to balance a variety of trial issues and topics that are of interest to our diverse membership. The difficulty, I fear, is how to decide which session to attend because this year we have a greater selection of excellent presentations from which to choose. Specifically, we have 30 invited talks this year compared to last year’s 15, and 100 contributed talks compared to last year’s 70. There is surely something for everyone!

Organizing the general meeting and the important pre-meeting workshops did not just happen – it was the culmination of a year of preparation by volunteers who served on our Program Committee (chaired by Dean Fergusson) and our Education Committee (chaired by Chris Coffey). I sincerely thank all of you for your hard and persistent work. The fruits of your labors are before us and they look delicious! And I certainly thank everyone presenting at this meeting, both people who have presented before and those who might be new at this. Your presentations and participation in this meeting are valued.

With the meeting being on the Pacific Rim, this year we identified special lectures on themes related to clinical trials in Asia. Starting off on Monday morning, the Curtis Meinert Lecture will be given by Anushka Patel from The George Institute in Australia and India and is entitled “Clinical Trials in Asia – Crouching Tiger, Hidden Dragon.” Then on Wednesday morning, the Founders Lecture will be given by Johan Karlberg from The University of Hong Kong and is entitled “Asian Clinical Trial Trends - by Type of Sponsor, Trial Phase, Disease Area and Country.” And in-between, on Tuesday afternoon, the SCT Trial of The Year Presentation will be given by Prasanta Tripathy from the organization Ekjut in India entitled “Community Mobilisation through Women’s Groups for Saving Maternal and Newborn Lives.”

But beyond attending and participating in the presentations, an important feature of our conferences has always been meeting with new and old friends. In addition to the lively interactions we usually have at our coffee breaks, luncheons, and receptions, there are special receptions again this year for our affinity groups. These groups represent areas of specialization that are important to our society and include information technology, clinical research associates, physician trialists, and members of industry or Health Canada/the FDA. This past year we also added affinity groups for Trialists working in Europe and Trialists working in Asia. If you belong to any of these groups, please join your colleagues at the affinity-specific receptions we have scheduled for 6:30 on Tuesday evening, right after the Trial of the Year presentation. (Also – if you have an idea for other affinity groups, please let me know!)

That’s the overall plan for our meeting. We have a lot going on and I cannot wait for it to begin. Have fun at the meeting and enjoy yourselves in vibrant Vancouver and beautiful British Columbia!

Robert P. Byington
SCT President, 2010-2011
SCT Officers & Board

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Theodore Colton (2014) – Boston University, Boston, MA
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Yves D. Rosenberg (2012) – National Institutes of Health, Bethesda, MD
Daniel Sargent (2011) – Mayo Clinic, Rochester, MN
David L. Sackett (2012) – Trout Research Centre, Markdale, Ontario, Canada
SCT Committees

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Education Committee
Christopher Coffey

Education Outreach
Robert P. Byington

Fellows Committee
Marian Fisher

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Robert Annechiarico

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J. Athene Lane

Trialists Working in Asia – Affinity Group
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James J. Dignam

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Editor, Clinical Trials: Journal of the Society for Clinical Trials
Steven Goodman

2011 Class of Fellows

The Board of Directors for the Society for Clinical Trials invites all meeting attendees to join in saluting the 2011 Fellows during the opening session on Monday, May 16 at 9:30 AM in the Regency Ballroom C-F.

Ivan S.F. Chan, PhD  Kenneth E. James, PhD  Wendy R. Parulekar, MD
Kay Dickersin, PhD  Theodore Karrison, PhD  Julie Weston, BScN, MSc
Robert J. Hardy, PhD  Pamela S. Moke, MSPH

Contributed Paper Session Moderators

Robert Anneciarico  Simon Day  Alison McDonald
Colin B. Begg  Dean Fergusson  Kristine Nelson
Marion Campbell  Susan Halabi  Wendy Parulekar
Ivan S.F. Chan  Jonathan Kimmelman  Tim Ramsay
Nicole Close  Beverly Koski  Domenic Reda
Jonathan Cook  Wendy McBee  Monica Taljaard
cancer Biomedical Informatics Grid (caBIG®) – Booth 1
The caBIG® community has developed a set of capabilities that help researchers connect with collaborators, enabling them to use and share diverse basic and clinical research data resources. These capabilities include data standards and applications to manage clinical trials and exchange data with commercial Clinical Data Management Systems.

OpenClinica – Booth 2
OpenClinica is the world’s fastest growing clinical trial software. Provided under a flexible open source model, OpenClinica provides a compelling alternative to proprietary, closed electronic data capture (EDC) and clinical data management (CDM) systems. The OpenClinica platform is trusted by leading industry, academic, and government research organizations worldwide.

EmpiriStat, Inc. – Booth 3
EmpiriStat is unique in our industry because we offer you more than unparalleled expertise and support for clinical trials and statistical analysis—we offer you a team of extraordinary people passionate about your work, genuinely enthusiastic about your goals, and are simply fun to work with. Visit us at www.empiristat.com.

Chapman & Hall/CRC Press – Booth 4
Chapman & Hall/CRC is a premier publisher of titles on clinical trials, biostatistics, and epidemiology. Please stop by our booth to review our newest and bestselling books, pick up free journal samples and take advantage of up to 50% conference discounts. Our acquisitions editor will be available to discuss new projects.

Syreon Corporation – Booth 5
Syreon is a leading provider of international clinical research for an elite portfolio of global pharmaceutical clients and emerging biotechnology corporations. Our ClinStream™ technology, medical expertise and global reach combine to reduce development costs, accelerate time to market, monitor health outcomes and ensure economic value in today’s competitive environment.

StudyManager – Booth 6
Since 1993, Seattle-based StudyManager has been providing innovative CTMS and EDC solutions to organizations who manage or conduct clinical trial research. StudyManager Evolve, our set of study management tools for pharmaceutical and medical device companies, biotechs, and CROs, accelerates study startup, providing a simpler, more intuitive way to efficiently manage studies.

NIH Office of Biotechnology Activities – Booth 7
The NIH has established the Clinical Research Policy Analysis and Coordination (CRpac) Program to serve as a focal point for ongoing harmonization, streamlining, and optimization of policies and requirements concerning the conduct and oversight of clinical research.

Quorum Review IRB – Booth 8
Quorum Review is an independent ethics review board that is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Our primary focus is to safeguard the rights and well-being of research participants. We provide sponsors, CROs, institutions, and sites with reliable, responsive service that ensures efficient study start-up and management. Website: www.QuorumReview.com / Email: clientrelations@quorumreview.com

SAGE – Booth 9
SAGE is a leading international publisher of journals, books, and electronic media for academic, educational, and professional markets. Since 1965, SAGE has helped educate a global community spanning a wide range of subject areas including business, humanities, social sciences, and science, technology, and medicine. Visit us at www.sagepub.com.
Exhibitor Map

Hyatt Regency
Vancouver
3rd Floor
SCT Corporate Sponsors &
Member Contributors

Thank you to our generous SCT Corporate Sponsors for the period May 2010 – April 2011:
Axiom Corporation
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Statistics Collaborative, Inc.

Member Contributors to SCT
We encourage members to consider making a tax deductible gift to support the non-profit activities sponsored by the Society. Your generous contributions help to fund the following programs:

Mary Karpers-Burke Member Sponsorship: Involves sponsoring one year of membership for a new member, in honor of Mary Burke, who served the Society as Coordinator for over 20 years.

General Fund: Allows the Society to use your gift flexibly to support various important activities.

Sylvan Green Scholarship Program: Provides funds for a physician clinical trialist to attend our annual meeting and present a paper (starting in 2011).

Supporting Federal Agencies since 1988

- Clinical research support, IT services, program management, training
- Successful past performance with DoD-sponsored Traumatic Brain Injury clinical research
- Service-Disabled Veteran-Owned Small Business and current 8(a) program participant

Heather Allore
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Andrew Avins
Stanley Azen
Cynthia Gyamfi Bannerman
Charles E. Barr
Colin B. Begg
Robert P. Byington
An-Wen Chan
Lisa Cox
Janet Darbyshire
Kay Dickersin
James J. Dignam
Dennis O. Dixon
Marian Fisher
Mae Gordon
Barbara Snyder Hawkins
C. Morton Hawkins
Ruth Kirby
Gordon Lan
Kelvin Lee
Anne S. Lindblad
Wendy Mack
Donald J. McMahon
Terrence E. Murphy
Yelena Novik
Wendy R. Parulekar
Nancy Payte
Janice Pogue
Philip C. Prorok
Frank W. Rockhold
Yves D. Rosenberg
Anne Ryan
David L. Sackett
Stanley H. Shapiro
Terri J. Shelton
Michael J. Sheridan
Tracy Howard Stone
Robert J. Temple
Barbara Tilley
Dennis Wallace
# Schedule of Events

**Sunday, May 15, 2011**

7:00 AM – 5:00 PM  
Registration – Plaza Foyer (2nd Floor)

**Pre-Meeting Workshops**

8:00 AM – 5:00 PM (Break 9:45 AM – 10:15 AM & 2:45 PM – 3:15 PM)

<table>
<thead>
<tr>
<th>Workshop P1 (Full day)</th>
<th>Essentials of Randomized Clinical Trials – Plaza A (2nd Floor)</th>
</tr>
</thead>
</table>

8:00 AM – 12:00 PM (Break 9:45 AM – 10:15 AM)

<table>
<thead>
<tr>
<th>Workshop P2</th>
<th>Workshop P3</th>
<th>Workshop P5</th>
<th>Workshop P6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and Analysis of Gene Expression Data</td>
<td>Overview of Non-Inferiority Study Designs</td>
<td>Trial and Site Management for Multi-Center Trials</td>
<td>Comparative Effectiveness Research – What Is It and How Can We Do It?</td>
</tr>
<tr>
<td>Georgia A (2nd Floor)</td>
<td>Plaza C (2nd Floor)</td>
<td>Georgia B (2nd Floor)</td>
<td>Plaza B (2nd Floor)</td>
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1:00 PM – 5:00 PM (Break 2:45 PM – 3:15 PM)

<table>
<thead>
<tr>
<th>Workshop P7</th>
<th>Workshop P8</th>
<th>Workshop P9</th>
<th>Workshop P10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood Methods for Measuring Statistical Evidence</td>
<td>Adaptive Clinical Trials</td>
<td>Challenges in Designing Small Clinical Trials</td>
<td>The Essentials of Clinical Data Management</td>
</tr>
<tr>
<td>Georgia A (2nd Floor)</td>
<td>Plaza C (2nd Floor)</td>
<td>Plaza B (2nd Floor)</td>
<td>Georgia B (2nd Floor)</td>
</tr>
</tbody>
</table>

5:15 PM – 7:30 PM  
SCT Board of Directors Meeting – Stanley (34th Floor)

5:30 PM – 6:30 PM  
Education Committee Meeting – Grouse (34th Floor)
## Schedule of Events

*All information/scheduling subject to change.*

### Monday May 16, 2011

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<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 AM – 5:00 PM</td>
<td>Registration – Plaza Foyer (2nd Floor)</td>
</tr>
<tr>
<td>8:00 AM – 5:30 PM</td>
<td>Exhibits, Posters – Regency Foyer &amp; Balmoral (3rd Floor)</td>
</tr>
<tr>
<td>8:30 AM – 8:45 AM</td>
<td>Welcome – SCT President, Robert P. Byington, Wake Forest University School of Medicine – Regency Ballroom C-F (3rd Floor)</td>
</tr>
<tr>
<td>8:45 AM – 9:30 AM</td>
<td>Curtis Meinert Lecture – Anushka Patel, MBBS, SM, PhD – Regency Ballroom C-F</td>
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<tr>
<td></td>
<td>Clinical Trials in Asia – Crouching Tiger, Hidden Dragon: The Challenges and Opportunities in India and China in Relation to Clinical Trials</td>
</tr>
<tr>
<td>9:30 AM – 10:00 AM</td>
<td>Presentation of Class of 2011 Fellows – Regency Ballroom C-F (3rd Floor)</td>
</tr>
<tr>
<td>10:00 AM – 10:30 AM</td>
<td>Break/Exhibits/Poster Prime Time – Regency Foyer &amp; Balmoral (3rd Floor)</td>
</tr>
<tr>
<td>10:30 AM – 12:00 PM</td>
<td>Invited Sessions I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>Session 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of Trial Size – How Large Should Our RCT Be?</td>
<td>Conducting Clinical Trials with Older Adults: Challenges and Strategies to Overcome Obstacles</td>
<td>Where Are We Going? Revision to Canadian Policy for Ethical Conduct of Research Involving Humans</td>
<td>Safety of Medicines: Clinical Trials and Pharmacovigilance</td>
<td>Opportunities and Challenges in the Design and Implementation of Enrichment Trials</td>
</tr>
<tr>
<td>Georgia A (2nd Floor)</td>
<td>Plaza B/C (2nd Floor)</td>
<td>Georgia B (2nd Floor)</td>
<td>Regency A (3rd Floor)</td>
<td>Regency B (3rd Floor)</td>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>12:00 PM – 1:30 PM</td>
<td>Lunch (Lunch included with registration) – Regency Ballroom C-F (3rd Floor)</td>
</tr>
<tr>
<td>1:30 PM – 3:00 PM</td>
<td>Contributed Paper Session I</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CPS 1A</th>
<th>CPS 1B</th>
<th>CPS 1C</th>
<th>CPS 1D</th>
<th>CPS 1E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Management</td>
<td>Information Technology</td>
<td>Patient Recruitment, Enrollment, and Retention</td>
<td>Quality Assurance and Monitoring</td>
<td>Surgical Trials</td>
</tr>
<tr>
<td>Georgia A (2nd Floor)</td>
<td>Regency A (3rd Floor)</td>
<td>Plaza B/C (2nd Floor)</td>
<td>Regency B (3rd Floor)</td>
<td>Georgia B (2nd Floor)</td>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>3:00 PM – 3:30 PM</td>
<td>Break/Exhibits/Poster Prime Time – Regency Foyer &amp; Balmoral (3rd Floor)</td>
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<tr>
<td>3:30 PM – 5:00 PM</td>
<td>Invited Sessions II</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 6</th>
<th>Session 7</th>
<th>Session 8</th>
<th>Session 9</th>
<th>Session 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-examining Randomization Strategies for Large, Multicenter Clinical Trials</td>
<td>Trials in Asia – Challenges and Opportunities</td>
<td>Conducting Trials in Low and Middle-Income Countries: Challenges and Steps Forward</td>
<td>Reporting of Clinical Trial Results at Clinicaltrials.gov: Key Scientific Issues</td>
<td>Missing Data in Clinical Trials</td>
</tr>
<tr>
<td>Georgia A (2nd Floor)</td>
<td>Regency A (3rd Floor)</td>
<td>Regency B (3rd Floor)</td>
<td>Plaza B/C (2nd Floor)</td>
<td>Georgia B (2nd Floor)</td>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>5:00 PM – 6:30 PM</td>
<td>SCT Program Committee Meeting – Cypress (34th Floor)</td>
</tr>
<tr>
<td>6:30 PM – 8:00 PM</td>
<td>Full Conference Reception – Regency Ballroom C/D (3rd Floor)</td>
</tr>
</tbody>
</table>
## Schedule of Events

*All information/scheduling subject to change.

### Tuesday May 17, 2011

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 AM – 5:00 PM</td>
<td>Registration – Plaza Foyer (2nd Floor)</td>
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<tr>
<td>8:00 AM – 5:00 PM</td>
<td>Exhibits, Posters – Regency Foyer &amp; Balmoral (3rd Floor)</td>
</tr>
<tr>
<td>7:50 AM – 8:50 AM</td>
<td>Contributed Paper Session II</td>
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<tr>
<td></td>
<td><strong>CPS 2A</strong>&lt;br&gt;Ethical Issues in Cluster Trials&lt;br&gt;– Plaza B/C (2nd Floor)</td>
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<tr>
<td></td>
<td><strong>CPS 2B</strong>&lt;br&gt;Ethical, Regulatory, Policy Issues&lt;br&gt;– Regency A (3rd Floor)</td>
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<td></td>
<td><strong>CPS 2C</strong>&lt;br&gt;HIV Design Issues&lt;br&gt;– Regency B (3rd Floor)</td>
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<tr>
<td></td>
<td><strong>CPS 2D</strong>&lt;br&gt;Patient Recruitment, Enrollment, and Retention&lt;br&gt;– Georgia B (2nd Floor)</td>
</tr>
<tr>
<td></td>
<td><strong>CPS 2E</strong>&lt;br&gt;Quality Assurance and Monitoring&lt;br&gt;– Georgia A (2nd Floor)</td>
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### 9:00 AM – 10:30 AM

<table>
<thead>
<tr>
<th>Session 11</th>
<th>Invited Sessions III</th>
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</thead>
<tbody>
<tr>
<td><strong>Design, Analysis and Monitoring of Clinical Trials: What if No Cox Model?</strong></td>
<td><strong>Session 12</strong>&lt;br&gt;U.S. Government-funded Clinical Trials in the European Union: Challenges and Lessons Learned&lt;br&gt;– Plaza B/C (2nd Floor)</td>
</tr>
<tr>
<td><strong>Regency A</strong> (3rd Floor)</td>
<td><strong>Session 13</strong>&lt;br&gt;Thomas Chalmers Scholarship Presentations&lt;br&gt;– Regency B (3rd Floor)</td>
</tr>
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</table>

### 10:30 AM – 11:00 PM

| Break/Exhibits/Poster Prime Time – Regency Foyer & Balmoral (3rd Floor) |

### 11:00 AM – 12:30 PM

<table>
<thead>
<tr>
<th>Invited Sessions IV</th>
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</thead>
<tbody>
<tr>
<td><strong>Session 16</strong>&lt;br&gt;Industry Statisticians: Part of the Problem, Part of the Solution or Innocent Bystanders in Peer-Reviewed Medical Literature?&lt;br&gt;– Georgia A (2nd Floor)</td>
</tr>
<tr>
<td><strong>Session 17</strong>&lt;br&gt;The Legal System: Evidence-Based Medicine’s Last Stand?&lt;br&gt;– Plaza B/C (2nd Floor)</td>
</tr>
<tr>
<td><strong>Session 18</strong>&lt;br&gt;Ethical Issues in Cluster Randomized Trials: Challenges and Preferred Solutions&lt;br&gt;– Georgia B (2nd Floor)</td>
</tr>
<tr>
<td><strong>Session 19</strong>&lt;br&gt;The CATT Study: A Milestone in Comparative Effectiveness Research&lt;br&gt;– Regency A (3rd Floor)</td>
</tr>
<tr>
<td><strong>Session 20</strong>&lt;br&gt;Challenges in Infectious Disease Clinical Trials Conducted in India and Southeast Asia&lt;br&gt;– Regency B (3rd Floor)</td>
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<thead>
<tr>
<th>12:30 PM – 1:50 PM</th>
<th>Lunch/SCT Business Meeting (Lunch included with registration) – Regency Ballroom C-F (3rd Floor)</th>
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</thead>
<tbody>
<tr>
<td>1:50 PM – 2:50 PM</td>
<td>Contributed Paper Session III</td>
</tr>
<tr>
<td><strong>CPS 3A</strong>&lt;br&gt;Facilitating Research&lt;br&gt;– Plaza B/C (2nd Floor)</td>
<td></td>
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<tr>
<td><strong>CPS 3B</strong>&lt;br&gt;Methodological Issues in Trials&lt;br&gt;– Regency A (3rd Floor)</td>
<td></td>
</tr>
<tr>
<td><strong>CPS 3C</strong>&lt;br&gt;Patient Safety&lt;br&gt;– Georgia A (2nd Floor)</td>
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<tr>
<td><strong>CPS 3D</strong>&lt;br&gt;Trial Design&lt;br&gt;– Georgia B (2nd Floor)</td>
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<tr>
<td><strong>CPS 3E</strong>&lt;br&gt;Trial Monitoring&lt;br&gt;– Regency B (3rd Floor)</td>
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| 2:50 PM – 3:20 PM  | Break/Exhibits/Poster Prime Time – Regency Foyer & Balmoral (3rd Floor) |

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9
Schedule of Events

3:20 PM – 4:50 PM

Invited Sessions V

**Session 21**
Improving Safety Notifications to Investigators and Patients – Evolving Practice, Alternatives, and FDA Perspectives
- Plaza B/C (2nd Floor)

**Session 22**
The Changing World of Data Management
- Regency A (3rd Floor)

**Session 23**
Frequentist, Bayesian and Likelihood Designs for a Phase II Cancer Trial with a Time-to-Event Endpoint: Head to Head Comparison of Three Philosophies of Trial Design
- Regency B (3rd Floor)

**Session 24**
Practical Application of Adaptive Treatment Strategies in Trial Design and Analysis
- Georgia A (2nd Floor)

**Session 25**
New Insights in Reporting Clinical Trials: From Protocol to Systematic Review and Beyond
- Georgia B (2nd Floor)

5:00 PM – 6:20 PM

Plenary Session: Trial of the Year/Project ImpACT – Regency Ballroom C-F (3rd Floor)

6:30 PM – 7:30 PM

Affinity Group Receptions:

- Information Technology
  - Plaza B (2nd Floor)

- Clinical Research Associates
  - Plaza C (2nd Floor)

- MD Clinical Trials
  - Georgia A (2nd Floor)

- Members of Industry or FDA
  - Georgia B (2nd Floor)

- Trialists Working in Europe
  - Regency A (3rd Floor)

- Trialists Working in Asia
  - Regency B (3rd Floor)

Wednesday May 18, 2011

7:00 AM – 11:00 AM
Registration – Plaza Foyer (2nd Floor)

8:00 AM – 8:45 AM

**Founders Lecture: Johan Karlberg, MD, PhD, BSc** – Regency Ballroom C-F (3rd Floor)
Asian Clinical Trial Trends, by Type of Sponsor, Trial Phase, Disease Area, and Country

9:00 AM – 10:30 AM

Contributed Paper Sessions IV

**CPS 4A**
Clinical Epidemiology
- Georgia A (2nd Floor)

**CPS 4B**
Hot Topics in Conducting Trials
- Plaza B/C (2nd Floor)

**CPS 4C**
Outcome Assessment Issues
- Georgia B (2nd Floor)

**CPS 4D**
Statistical Issues
- Regency A (3rd Floor)

**CPS 4E**
Trial Designs
- Regency B (3rd Floor)

10:30 AM – 10:45 AM
Break – Plaza Foyer (2nd Floor)

10:45 AM – 12:15 PM

Invited Sessions VI

**Session 26**
Harmonizing the Human-Computer System Relationship to Optimize Trial Operation Management in the Era of Web-based CTMS
- Georgia A (2nd Floor)

**Session 27**
Update on Results from the Clinical Trials Transformation Initiative
- Plaza B/C (2nd Floor)

**Session 28**
New Developments/ Emerging Issues in the Design and Analysis of Clinical Trials in Asia
- Georgia B (2nd Floor)

**Session 29**
Assessing Biosimilarity of Follow-on Biologics
- Regency A (3rd Floor)

**Session 30**
Evolving Role of Data Safety Monitoring Board Members for Oncology Trials in the 21st Century
- Regency B (3rd Floor)

*All information/scheduling subject to change.*
Pre-Conference Workshops
May 15, 2011

Full Day Workshop
Workshop P1 8:00 AM – 5:00 PM
Essentials of Randomized Clinical Trials

This full-day pre-conference workshop is an overview of some essential concepts related to the design, conduct and analysis of clinical trials. The workshop is intended for those with little previous experience or formal training in clinical trials as well as those who have some basic clinical trial experience but desire a better fundamental understanding of the methodological principles and concepts involved in clinical trials. No prior knowledge of biostatistics is needed. The first half of the workshop will introduce participants to some key principles associated with the design and conduct of clinical trials. Topics to be covered include the rationale for randomized clinical trials, key design and methodological issues, such as choice of eligibility criteria, a control group, randomization and blinding-related issues, and how to define objectives and end-points for a trial. This first part of the workshop will cover basic principles of data collection, reporting, and quality control as well as principles of project management. The second half of the workshop will provide an overview of statistical principles and methodologies commonly utilized in clinical trials. Topics to be covered include choice of endpoints, sample size computation, methods for treatment allocation and stratification, procedures for monitoring a trial, and how to analyze the results from randomized clinical trials.

Attendees will learn to be able to describe the essential elements of a clinical trial, essential principles of project management of a multicenter clinical trial, describe key statistical concepts and their application to the validity and interpretation of clinical trial results, and use this knowledge to contribute as a researcher or collaborator in the successful conduct of a clinical trial. In addition, attendees should be able to read the clinical trials literature critically.

Faculty:  
Dixie Ecklund, University of Iowa  
Susan Halabi, Duke University  
Laura Lovato, Wake Forest University  
Michele Melia, Jaeb Center for Health Research  
Yves Rosenberg, NHLBI/NIH

Workshop Organizer: Yves Rosenberg, NHLBI/NIH

Half Day Workshops – Morning
Workshop P2 8:00 AM – 12:00 PM
Design and Analysis of Gene Expression Data

Many Phase 2 and 3 clinical studies have begun to incorporate DNA microarrays and other high throughput biotechnologies as a means of investigating the potential associations between high-dimensional molecular data and clinical outcome. Because of this, there are great expectations on the use of this technology to develop and validate molecular biomarkers with prognostic and diagnostic potential in clinical oncology and other complex diseases.

This workshop provides an overview of the many considerations and challenges in incorporating microarray in Phase 2 and 3 clinical trials, including:

- A brief summary of the central dogma of biology and gene expression.
- Microarray platforms and the pre-processing methods to conduct quality control and to generate gene expression data.
- The detection of associations with clinical outcomes at the gene- and pathway-level.
- Multiple testing considerations critical to high-dimensional data.
Unsupervised learning algorithms for clustering samples/subjects

Supervised learning algorithms for building predictive models of patient characteristics and clinical outcomes

Clinical trial designs for retrospective and prospective validation of microarray-based biomarkers

Illustrations of the above topics and analytic approaches will be drawn from examples of cancer clinical trials and microarray data, and will also highlight some of the potential pitfalls when using these technologies. All pre-processing, visualization and analysis will be performed using statistical and genomic packages in R/Bioconductor. The code used to generate all results presented in the workshop will be made available to the attendees.

The workshop faculty members have experience in designing, implementing, and analyzing gene expression microarrays in single and multi-institutional trials in oncology. The faculty will share their extensive experience with the attendees of the workshop.

**Faculty:** William Barry, Duke University
Herbert Pang, Duke University

**Workshop Organizer:** Susan Halabi, Duke University

**Workshop P3** 8:00 AM – 12:00 PM

**Overview of Non-Inferiority Study Designs**

This workshop gives an overview of many of the issues faced by those designing, running, analyzing, presenting, and interpreting studies aimed at showing that a new therapy is ‘no worse than’ (from a practical point of view) an existing therapy. Such trials are becoming increasingly common and – although not yet finalized – a draft guidance document from the U.S. Food and Drug Administration (FDA) will help to settle many of their uncertainties and requirements. The presentation will be at a non-technical level but requires, as a pre-requisite, a basic level of understanding of the fundamental principles of clinical trials. It is relevant both to statisticians and non-statisticians because the issues to be covered are more at a concept level than a detailed analysis level. Frequent cross-reference to the draft FDA guidance, as well as to European regulatory guidance, will be given. The course is relevant to those in the pharmaceutical sector as well as those from government and academia; it will include scientific and regulatory issues, with examples taken from the U.S. and Europe.

At the end of the workshop, attendees should understand the purpose and potential benefits of non-inferiority studies and how they differ from superiority studies. Attendees should also understand the extra difficulties associated with these types of studies, over and above those of superiority studies including such points as assay sensitivity, choice of control group, choice of population to study/analyze, choice of endpoint, and choice of non-inferiority margin.

**Faculty:** Simon Day, Roche Products Ltd, UK
Nicole Close, EmpiriStat Inc.

**Workshop Organizer:** Devin J. Hunt, EmpiriStat Inc.
Workshop P5 8:00 AM – 12:00 PM
Trial and Site Management for Multi-Center Trials

Successful completion of multi-site clinical trials depends entirely on the performance of the clinical sites. They must recruit patients and complete data in a timely manner. This workshop will present information on how to manage your trial and clinical sites to ensure this. Practical examples will be presented for each topic and discussion with workshop participants will be encouraged.

Our international workshop faculty members have experience in coordinating national and international trials, as well as recruiting patients and managing activities at clinical centers. They have worked in a variety of settings and will bring their varied experiences to this workshop.

Topics to be covered include:

- Identifying and assessing the suitability of clinical sites
- Paperwork required from sites to participate
- Handling payments to the sites, including different types of contracts
- Staffing requirements at the coordinating centre
- Training staff at the clinical sites, including information the coordinating centre should provide
- Techniques for interacting effectively with clinical sites
- Staff motivation at clinical sites
- Patient recruitment and retention strategies
- Data collection systems and techniques to ensure timely completion
- Study record keeping suggestions
- Study close down process
- Publication arrangements and policies with clinical sites

Faculty:  
Alison McDonald, University of Aberdeen  
Julie Weston, University of Toronto  
Carole White, University of Texas Health Science Center-San Antonio

Workshop Organizer:  
Julie Weston, University of Toronto

Workshop P6 8:00 AM – 12:00 PM
Comparative Effectiveness Research (CER): What Is It and How Can We Use It?

This workshop will define comparative effectiveness research, provide a brief background of the history of this type of research, help attendees understand where it fits in the spectrum of research, and why it is such a “hot topic”. Four different study methodologies (systematic review/meta-analysis, modeling/decision analysis, analysis of observational data from registries and electronic health records, clinical trials) that could be used for CER will be presented using real examples with commentary by a discussant. At the conclusion of the presentations, a discussant will be able to define and describe each methodology as it relates to CER. Following the presentation of the research methodologies, an interactive session will be held with the discussant and the presenters in which the key inclusion and exclusion criteria of CER and a hierarchy of evidence will be defined and debated.

By the end of this workshop, participants will be able to:

1. Define comparative effectiveness research (CER)
2. Place CER on the spectrum of clinical research
3. Discuss the pros and cons of various research methodologies for answering questions of comparative effectiveness
4. List inclusion and exclusion criteria of CER research
5. Provide arguments for and against a hierarchy of evidence for question of CER

**Faculty:**
- Aslam H. Anis, University of British Columbia
- Stephen Chia, University of British Columbia
- Janet Coffman, University of California – San Francisco
- Kay Dickersin, Johns Hopkins University
- Katherine Newton, Group Health Research Institute

**Workshop Organizer:**
- Denise Bonds, NHLBI/NIH
- Wendy Parulekar, NCIC Clinical Trials Group

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**Half Day Workshops – Afternoon**

**Workshop P7 1:00 PM – 5:00 PM**

**Likelihood Methods for Measuring Statistical Evidence**

Likelihood methods for measuring statistical evidence have evolved slowly since they were first introduced by R.A. Fisher in the early 1920’s. Nearly a century later, the Likelihood paradigm has matured enough to warrant careful consideration. Likelihood methods are the natural compromise between Bayesian and frequentist approaches; they retain desirable properties of both paradigms (irrelevance of sample space, good performance probabilities) while shedding undesirable ones (dependence on prior distributions, ad-hoc adjustments to control error probabilities).

This workshop will present the philosophy and mechanics of likelihood methods for measuring statistical evidence and contrast this approach with today’s standard Frequentist and Bayesian approaches. The focus of the workshop will be on illustrating likelihood methods in real-world examples and understanding their operating characteristics. The likelihood resolution of multiple comparisons and multiple looks controversies will be discussed and demonstrated. In particular, we examine how likelihood methods can resolve these controversies without resorting to ad-hoc adjustments of the tail area probability yet maintain excellent frequentist properties. The goal is to generate familiarity with these methods, their limitations and advantages, and note recent advancements for clinical trials. Connections between likelihood ratios, p-values, Bayes-factors, and posterior probabilities will be discussed. Mathematical and computational details will be kept to a minimum; the focus will be on key concepts and examples.

Highlights of the workshop include: Proper use and interpretation of results from hypothesis tests, significance tests, and Bayesian methods (Bayes-factors, posterior probabilities); the three questions for choosing a foundational approach; law of likelihood; likelihood principle; the three evidential quantities essential for measuring and understanding statistical evidence; the connection between sample size and the probabilities of misleading, weak, and strong evidence; likelihood methods for composite hypotheses and the probabilities of being led astray; multiple endpoints in a likelihood context (multiple comparisons problem); re-examining accumulation evidence during the course of a clinical trial with likelihood methods (multiple looks problem); likelihood study designs for 2-stage Phase 2 trials; likelihood re-analyses of several well known multi-center trials.

Prerequisites include a general understanding of statistical inference (e.g., hypothesis testing, confidence intervals, Bayes theorem, sensitivity & specificity, positive & negative predictive value, etc.), observational studies, and clinical trials. The majority of material is accessible to participants who have taken one introductory semester of statistics that included regression concepts.

**Faculty:**
- Gregory S. Ayres, Vanderbilt University
- Jeffrey D. Blume, Vanderbilt University

**Workshop:**
- Jeffrey D. Blume, Vanderbilt University
Workshop P8  1:00 PM – 5:00 PM
Adaptive Clinical Trials

Adaptive clinical trials – trials in which key design parameters are modified according to pre-specified decision rules during the course of the trial in response to accumulating data from the trial – may be more efficient, ethically acceptable and, if properly designed and executed, accurate than traditional designs. However, the design of such trials is inherently more complex than traditional approaches and must precisely define the planned adaptations a priori. In addition, simulation has an important role in evaluating the operating characteristics of adaptive trials. The implementation of adaptive trials introduces additional complexities in logistics, data availability, randomization, drug supply, and interactions with the sponsor and independent data and safety monitoring boards (DSMBs). The rapid proliferation of adaptive designs, and inconsistent use of terminology, has created confusion about the similarities and, more importantly, the differences among the techniques. In this workshop, presenters with a broad range of experience in the conduct of these trials will address conceptual, statistical, and logistical issues in the design, implementation, and analysis of adaptive clinical trials.

First, Dr. Lewis will discuss logistical and practical issues in composition, function, and interactions with all participants in the trial’s design and execution and provide an example from a Phase 2 drug trial. He will describe the information flow necessary for an efficient trial and rapid and timely adaptations but also to ensure blinding. Then, he will describe a trial where a DSMB used pre-specified rules developed in conjunction with the sponsor to drop an arm during a dose-finding trial. Then, Dr. Connor will describe a dual endpoint (efficacy and safety) adaptive Bayesian design of a medical device. This trial design will be used to illustrate how interim data and a Bayesian longitudinal model can be used to calculate predictive probabilities that are used to identify the optimal trial size during the course of the trial.

Attendees should be conversant in the fundamentals of clinical trial design and methodology, but no foundational knowledge of Bayesian statistics or adaptive designs is required. The expected audience is statisticians, clinicians involved in trials, and other clinical trialists interested in adaptive designs. After the course, attendees will understand the role of adaptive trials and possess the foundation for their design, implementation, and interpretation.

Faculty: Jason Connor, Berry Consultants
Roger J. Lewis, Harbor-UCLA Medical Center

Workshop Organizer: Susan Halabi, Duke University

Workshop P9  1:00 PM – 5:00 PM
Challenges in Designing Small Clinical Trials

The term ‘small clinical trial’ does not mean the same thing to all investigators. A small clinical trial could involve a Phase 3 trial in the orphan or rare disease setting. For others, a small clinical trial might involve an early phase trial for other disease areas. In either case, small clinical trials present unique challenges to the clinical trials community. Summary statistics from small trials are often imprecise so that the trials may have adequate power to detect only large effects of interventions. Furthermore, many standard statistical techniques are based on large sample assumptions and do not have desirable properties in the small sample setting. As a consequence, the importance of adequate study planning is magnified in small clinical trials. Hence, it is critically important to have a true collaboration between study investigators and statisticians.

This workshop will review some specific designs that are useful for each type of small clinical trial. Topics to be covered include the use of parallel group designs, crossover designs, add-on designs, N-of-1 designs, sequential designs, and ranking/selection designs. Statistical methods appropriate for these designs will be discussed. The workshop will also examine the utility and potential benefits associated with the use of adaptive designs in the small trial setting.
Although the focus of the workshop is on issues related to design, the target audience for this workshop is any clinical investigator, statistician, or coordinator that is involved in the planning, conduct, or analysis of small clinical trials. Attendees should have a basic understanding of clinical trial designs and standard statistical analysis techniques.

**Faculty:** Christopher Coffey, University of Iowa
Janet Wittes, Statistics Collaborative

**Workshop Organizer:** Christopher Coffey, University of Iowa

### Workshop P10 1:00 PM – 5:00 PM

**The Essentials of Clinical Data Management**

This workshop will provide real-world experience to familiarize participants with the specific tasks involved in clinical data management. Taught from the perspective of a data manager and database programmer, participants will examine the steps, processes, regulatory requirements and best practices for:

- the role of a data manager within the clinical study team
- reviewing a study protocol and other essential study documents
- designing, developing, and testing case report forms (CRF)
  - paper CRFs
  - electronic CRFs (eCRF)
- developing data management plans, data validation plans, and edit specifications
- designing and reviewing a clinical database
- medical coding processes
- performing frequent quality control procedures including data review, table and listing review, and review of the integrated clinical and statistical final study report.

This course applies to personnel entering into the clinical data management field, personnel needing a refresher course, or personnel who interact with data managers and need to understand data management’s responsibilities. This course would also benefit anyone who is involved in the planning and preparing of a clinical trial, conducting a clinical trial, or has management responsibility (direct or indirect) for clinical trials.

**Faculty:** Devin J. Hunt, EmpiriStat Inc.
Jill Kuennen, University of Iowa

**Workshop Organizers:** Devin J. Hunt, EmpiriStat Inc.

**5:15 PM – 7:30 PM**
SCT Board of Directors Meeting

**5:30 PM – 6:30 PM**
Education Committee Meeting
Monday, May 16, 2011

All information subject to change

7:00 AM – 5:00 PM  Registration

8:00 AM – 5:30 PM  Exhibits

8:30 AM – 8:45 AM  Welcome – SCT President, Robert P. Byington, PhD
Wake Forest University School of Medicine, Winston-Salem, NC

8:45 AM – 9:30 AM  Curtis Meinert Lecture – Anushka Patel, MBBS, SM, PhD
Clinical Trials in Asia – Crouching Tiger, Hidden Dragon: The Challenges and Opportunities in India and China in Relation to Clinical Trials

9:30 AM – 10:00 AM  Presentation of Class of 2011 Fellows

10:00 AM – 10:30 AM  Break/Exhibits/Poster PrimeTime

10:30 AM – 12:00 PM  Invited Session 1
Determination of Trial Size – How Large Should Our RCT Be?
Central to the validity of a RCT is a calculation of the number of participants needed (the sample size). This provides reassurance that the trial will be able to identify a difference between groups of a particular magnitude. From both a scientific and ethical standpoint, selecting an appropriate “target” difference is a key concern. In contrast to purely statistical approaches for sample size calculation, determination of the target difference has received remarkably little attention. A variety of approaches have been proposed including clinical (e.g. “minimal clinically important difference”), evidence synthesis (e.g. assessing the new study’s potential impact upon a meta-analysis) and health economics (e.g. value of information analysis). This session will present various perspectives on this issue and provide the opportunity for discussion.

Chair:  Dean Fergusson, Ottawa Hospital Research Institute
Organizer:  Jonathan Cook, University of Aberdeen
Speakers:
Jonathan Cook, University of Aberdeen — Introduction to topic
Jitendra Ganju, Amgen Inc. — Industry perspective
John Norrie, University of Glasgow — Trialist’s perspective
Andy Willan, University of Toronto — Health economics perspective

10:30 AM – 12:00 PM  Invited Session 2
Conducting Clinical Trials with Older Adults: Challenges and Strategies to Overcome Obstacles
Older adults bear the greatest burden of illness and disability, and commonly have multiple competing health conditions yet are typically excluded from clinical intervention trials. This session outlines the challenges of designing, conducting and analyzing clinical trials with older adults. There is a growing emphasis by the NIH to have older adults with multiple morbidities participate in clinical trials as they take the majority of medications, have many hospitalizations and medical procedures and account for a large portion of the health care budget. Yet they are routinely excluded for the trials that if successful may result in those very treatments being given to them.

Each invited speaker has experience working in large clinical trials with older adults and we bring together experience from academia and the Veterans Administration.

Organizer:  Heather Allore, Yale University School of Medicine
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Speakers: Richard Marottoli, Yale University School of Medicine — The Clinical Importance of Including Older Participants in Trials
Peter Guarino, Department of Veteran’s Affairs (VA) Cooperative Studies Program — Recruitment, retention and maintaining treatment adherence of older adults in clinical trials: Experience in VA Cooperative Studies of Alzheimer’s disease and stroke rehabilitation.
Peter Van Ness, Yale University School of Medicine — Conducting Comparative Effectiveness Trials with Older Adults: Practical and Methodological Issues

10:30 AM – 12:00 PM Invited Session 3
Where Are We Going? Revision to Canadian Policy for Ethical Conduct of Research Involving Humans

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) sets forth the policy of Canadian Research Councils with regard to the ethical conduct of research involving humans. The Policy applies to all research carried out at institutions receiving funds from the Councils, irrespective of the source of funding. Accordingly some research undertaken for regulatory purposes has been a source of contention as selected TCPS policies are more stringent than their regulatory counterparts.

Over the course of the past several years, a revised edition of the TCPS has been under development. This second edition is described as a major revision constituting the first substantive changes to the Policy since its adoption in 1998. This session will examine the evolution of Canadian policies for randomized controlled trials as well as their relationship to other international and national policies.

Organizer: Stanley H. Shapiro, McGill University

Speakers: Susan Zimmerman, Canadian Interagency Secretariat on Research Ethics
Jonathan Kimmelman, McGill University
Robert Peterson, Drug Safety and Effectiveness Network (DSEN) of the Canadian Institutes of Health Research (CIHR)
Liza Dawson, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Discussant: Stanley H. Shapiro, McGill University

10:30 AM – 12:00 PM Invited Session 4
Safety of Medicines: Clinical Trials and Pharmacovigilance

Assessing safety and assessing harms are difficult tasks except when there are obvious dangers. Assessing efficacy is not always easy – but there are much better standards to follow and the important contrast between pre-specified intentions and post-hoc findings is well understood and accepted. Also well accepted is the notion of hierarchies of evidence (e.g. Green SB, Byar DP, 1984 “Using observational data from registries to compare treatments: the fallacy of omnimetrics.” Statist Med 3:361–370).

In this session we want to contrast the sources of useful data for assessing safety rather than efficacy and explore the hierarchies of evidence that may exist for safety data. Clearly, pre-approval studies will never match the size of post-approval exposure (whether for rare diseases or very common ones). However, benefit–risk assessments should always be ongoing, implying that new data and experience should be continuously updating our perspectives of a product. The issues of quantity of evidence and quality of evidence need to be considered. Thus even if the hierarchy of evidence may be different for safety and efficacy, we have to hold to a standard of scientific rigor in assessing signals of risk.

Organizers: Frank Rockhold, GlaxoSmithKline
Simon Day, Roche Products Ltd
Monday, May 16, 2011

**Speakers:**
- Larry Lynd, University of British Columbia
- Robert O’Neill, U.S. Food and Drug Administration
- Robert Lindblad, The EMMES Corporation

**10:30 AM – 12:00 PM  Invited Session 5  
Opportunities and Challenges in the Design and Implementation of Enrichment Trials**

Increased advances in understanding the roles of molecular and genetic pathways in carcinogenesis are leading to the development of novel therapies that target these pathways. Before embarking on a trial of a targeted agent that either prospectively stratifies or selects patients (i.e., “enrichment”) based on the relevant molecular marker, a strong scientific rationale is necessary. In this session, issues in the design and implementation of molecular marker-based strategies in Phase II trials in oncology will be discussed. In addition to describing the statistical design selected to evaluate efficacy of the targeted agent, these talks will also highlight the scientific rationale and compelling clinical data including validation of the target pathways at the time the trials were designed. Statistical and logistical issues relating to the conduct and monitoring of such trials will also be discussed. In addition, real life examples using both frequentist and Bayesian approaches will be provided. An assessment of where and when enrichment designs may be an appropriate option will be discussed.

**Organizers:**
- Susan Halabi, Duke University
- Rosemarie Mick, University of Pennsylvania

**Speakers:**
- Susan Halabi, Duke University — Enrichment Trials: Fact or Fiction
- Philip Febbo, University of California San Francisco — The Use of Gene Expression-Based Assays to Guide Therapy
- Daniel Sargent, Mayo Clinic — Real World Experiences in Clinical Trials involving Predictive Biomarker Validation
- Michael LeBlanc, SWOG Statistical Center — Soft Enrichment for Phase II designs
- Cheryl Jones, Genentech — Patient Enrichment and Trial Design Strategies for Interrogating a Predictive Diagnostic Hypothesis

**Discussant:**
- Gary Rosner, Johns Hopkins University

**12:00 PM – 1:30 PM  
Lunch (Lunch included with registration)**

**1:30 PM – 3:00 PM  
Contributed Paper Sessions I  
Session 1A: Data Management**

**Moderator:** Robert Annechiarico

- **1:30 PM 01**  
  Duplicate Identification Using Non-Sensitive Information; Zhibao Mi, VA Cooperative Study Program

- **1:45 PM 02**  
  Participant Data Entry for a Web Based Data Management System; Leah Griffin, Wake Forest University School of Medicine

- **2:00 PM 03**  
  A Secure Website for Participant Submission of Follow-up Data; Jo Ann Hartline, Cancer Research And Biostatistics

- **2:15 PM 04**  
  Data Collection and Storage for Online Screening Prior to Consent; Letitia Perdue, Wake Forest University Health Sciences

- **2:30 PM 05**  
  Challenges of Creating and Managing Standards (Common Data Elements) for Use in Clinical Trials; Patti Shugarts, KAI Research, Inc., an Altarum Company

- **2:45 PM 06**  
  Developing Statistical Standards in an Academic Data Coordinating Center; Amy Donaldson, University of Utah
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Session 1B: Information Technology  
**Moderator:** Kristine Nelson  
1:30 PM 07 Electronic Health Record and Clinical Trials: Advantages and Data Quality Issues; Reza Rostami, Duke Clinical Research Institute  
1:45 PM 08 Metadata as the Key to Semantic Interoperability in Clinical Data Systems; Brian Campbell, EMMES Corporation  
2:00 PM 09 Exploring a Dataset for Proactive Identification and Overlap Checking of Planned Policy Relevant Clinical Trials; Andrew Cook, University of Southampton, UK  
2:15 PM 10 The Effect of Short Messaging Service (SMS) Use for Subject Compliance in Clinical Trials; Keiko Sing, EmpiriStat, Inc.  
2:30 PM 11 Integration of Site Performance Monitoring Module in Web-Based CTMS for a Global Trial; Jaemyung Kim, Medical University of South Carolina  
2:45 PM 12 A Streamlined Process for Electronic Case Report Form Development; Lemuel Waitman, The University of Kansas Medical Center

Session 1C: Patient Recruitment, Enrollment, and Retention  
**Moderator:** Dean Fergusson  
1:30 PM 13 Experiences of the NINDS Clinical Research Collaboration with the use of a Virtual Coordinator; Carolyn Burke, The EMMES Corporation  
1:45 PM 14 Retention Strategies, Methodology and Considerations: An Example from a 3.5 Year Prospective, Closed, Combined Community/Workplace Clinical Epidemiological Study in Kenya; Nicole Close, EmpiriStat, Inc.  
2:00 PM 15 Intervention to Improve Recruitment to Randomized Controlled Trials; Jenny Donovan, University of Bristol  
2:15 PM 16 Dynamic Evolution of the Study Coordinator Role: The 27 Year Experience in DCCT/EDIC; Patricia Cleary, The George Washington University  
2:30 PM 17 Recruitment Methods Employed in the National Lung Screening Trial (NLST); Pamela Marcus, National Cancer Institute  
2:45 PM 18 Mid-Recruitment Trial Redesign to Incorporate Genetic Sub-Types; Sarah Brown, University of Leeds

Session 1D: Quality Assurance and Monitoring  
**Moderator:** Beverly Koski  
1:30 PM 19 The Potential for Central Monitoring Techniques to Replace On-Site Monitoring in Clinical Trials: A Review of Monitoring Findings from an International Multi-Centre Clinical Trial; Julie Bakobaki, Medical Research Council Clinical Trials Unit  
1:45 PM 20 Academic Trials and the Challenge of Sponsor Responsibility; Jochen Dress, University of Cologne  
2:00 PM 21 Peer Review Intervention for Monitoring and Evaluating Sites that Improved Randomised Controlled Trial Conduct and Performance; J. Athene Lane, University of Bristol  
2:15 PM 22 Harmonized Standard Operating Procedures for Academic Trials; Heike Moenkemann, University of Cologne
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2:30 PM 23 Solutions for Monitoring Medical Record Abstraction Quality in a Multi-Center Study; Nancy Payte, Westat

2:45 PM 24 A Web-Based Study Product Verification Utility for Blinded Treatment of Food Allergy Subjects; Daniel Rosenberg, The EMMES Corporation

Session 1E: Surgical Trials
Moderator: Jonathan Kimmelman

1:30 PM 25 Oncologic Outcomes of Laparoscopic and Open Colorectal Cancer Surgery: Meta-analysis and Correlation with Expert Opinion; Guillaume Martel, The Ottawa Hospital, University of Ottawa

1:45 PM 26 Statistical Issues in the Design of Randomised Surgical Trials: A Practical Example of the Possible Solutions; Helen Marshall, University of Leeds

2:00 PM 27 No Large Differences Among Centers in a Multi-Center Neurosurgical Clinical Trial; Emine Bayman, The University of Iowa

2:15 PM 28 Trials in Surgery: Evaluating a Simple or a Complex Intervention?; Marion Campbell, University of Aberdeen

2:30 PM 29 A Mixed Methods Study to Assess the Success of Blinding in Surgical Randomised Controlled Trials; Caroline Boulind, University of Bristol

2:45 PM 30 Adopting New Surgical Devices into Clinical Practice: Contrasting Roles of HTA Organisations in Canada; Sue Ross, University of Calgary

3:00 PM – 3:30 PM Break/Exhibits/Poster Prime Time

3:30 PM – 5:00 PM Invited Session 6
Re-examining Randomization Strategies for Large, Multicenter Clinical Trials

It is well known that randomization is a key component of good clinical trial design. When correctly implemented, randomization minimizes selection bias and balances known and unknown prognostic factors. Among the several available randomization methods in the literature, the majority of trials tend to implement the permuted block randomization stratified by known prognostic factors. However there are several other available randomization schemes that may offer better performance properties. In this session, the speakers will examine various randomization algorithms, discuss selection bias and the value of baseline covariate balance, and review the recent progress in randomization algorithm development and implementation. The goal is to provide guidance on implementing these available methodologies to a wide audience of clinical trialists and to open the discussion on what is a viable randomization scheme.

Organizers: Valerie Durkalski, Medical University of South Carolina
Yuko Palesch, Medical University of South Carolina

Chair: Valerie Durkalski, Medical University of South Carolina

Speakers: Wenle Zhao, Medical University of South Carolina — Quantitative Comparison of Randomization Designs in Sequential Clinical Trials
Kathryn Tucker, Statistics Collaborative — Pitfalls in Implementing Dynamic Allocation Algorithms
Jason Connor, Berry Consultants — Response-Adaptive Randomization

Discussant: Roger Lewis, UCLA Medical Center
Invited Session 7
Trials in Asia – Challenges and Opportunities

In this session we propose to address several emerging methodological issues regarding undertaking randomised trials in Asia. The session will involve 3 presentations and a review by a discussant before inviting more general contributions from the session participants.

Session Objectives

• To consider methodological aspects of trials from China and India, and compare these with trials from North America and Western Europe.

• To consider the methodological challenges in designing and interpreting trials across cultural diversity.

• To consider the challenges for health policy makers in undertaking and interpreting health economic analyses across cultural and economic diversity.

Organizer: Nick Freemantle
Chair: John Wood
Speakers:
Dalu Zhang — Quality of Trials in Emerging Economies
Nick Freemantle — Addressing Country Effects
Stirling Bryan — Health Policy and Health Economics
John Wood — Summary of Main Points and Discussion

Invited Session 8
Conducting Trials in Low and Middle-Income Countries: Challenges and Steps Forward.

Conducting clinical trials in low and middle income countries (LMIC) is challenging due to a variety of issues including competing priorities, lack of infrastructure, transient communities, administrative complexities and political instabilities. This session will address examples of clinical trial challenges in LMIC settings. While challenges for clinical trials are a pressing reality, there are many examples of successful and important clinical trials that have influenced policy changes and improved the health of those in the local setting. This aims to overcome perceived barriers to developing clinical trials in LMIC settings and lay groundwork to develop local capacity to conduct locally relevant trials.

We will use examples of conducting clinical trials of HIV/AIDS treatment and prevention in Kenya, South Africa and Thailand. We will address the political complexities of these settings and the challenges of funding allocation from high income research institutions transferring to institutions in LMICs.

Chair: Edward Mills
Speakers:
Richard Lester, University of British Columbia — Conducting an RCT During Civil Violence in Kenya
Thomas Kerr, University of British Columbia — Conducting Research on Drug Users in Thailand During the War on Drugs
Lehana Thabane, McMaster University — Transferring of Funding and Financial Setups in Developing Countries

Invited Session 9
Reporting Of Clinical Trial Results at Clinicaltrials.Gov: Key Scientific Issues

It is 3 years after the Food and Drug Administration Amendments Act of 2007 (FDAAA) expanded clinical trial registration requirements and 2 years after the requirement to report clinical trial results at ClinicalTrials.gov took effect. As of September 2010, the registry contains over 96,000 clinical studies and over 3,000 submitted results records. On average, 300-350 new protocol and 35 – 40 new results registrations are received each week. Prior to public posting, submissions are reviewed for completeness, internal consistency and obviously
invalid information. The enhanced registry and results database is providing new opportunities to assess important aspects of ongoing and completed research, and is also providing a window into the conduct and analysis of clinical trials. During this session, overall findings about the clinical research enterprise will be reviewed including data on condition, intervention, study design, and sponsor type. In addition, the following key issues related to communication of results information in a structured, public database will be considered from the viewpoints of the database administrator, researcher, and public user:

- Quality of submitted results entries. Although some errors in entries reflect the fact that the investigator and statistician were not involved with results submission, others reflect a lack of understanding of basic concepts of trial design and clinical epidemiology among key trial personnel (e.g., the difference between a continuous and categorical outcome measure).
- Specification and number of primary outcome measures. The finding that many trials have five or more primary outcome measures, and the fact that the level of specification at the time of registration is quite variable. We have determined that there is lack of agreement within the community of trial investigators about these fundamental issues. The implications for the statistical analysis and interpretation of trial results will be discussed.

**Organizer and Chair:** Deborah A. Zarin, ClinicalTrials.gov

**Speakers and Discussants:**
- Jorge Tavel, National Institute of Allergy and Infectious Diseases, National Institutes of Health
- Jane Lindsey, Center for Biostatistics in AIDS Research, Harvard School of Public Health

3:30 PM – 5:00 PM  
**Invited Session 10**  
**Missing Data in Clinical Trials**

In early 2009, FDA asked the National Academies to convene an expert committee on missing data in clinical trials. The final report of that committee, entitled The Prevention and Treatment of Missing Data in Clinical Trials, was published late in 2010.

The session will focus on the content of the report, especially the recommendations of the committee and anticipated impact on clinical trials, particularly in the regulatory setting. Specific areas of discussion will include:

- Reducing the impact and frequency of missing data through trial design,
- Reducing the frequency of missing data through trial strategies
- Utility of various methods for drawing inferences from incomplete data
- Importance of prespecifying methods of analysis, identifying and justifying assumptions
- Role of sensitivity analyses in handling missing data

**Organizer:** Jay P. Siegel, Johnson & Johnson

**Speakers:**
- James Neaton, University of Minnesota
- Kay Dickersin, Johns Hopkins University
- Scott Emerson, University of Washington
- Robert Temple, U.S. Food and Drug Administration
- Robert O’Neill, U.S. Food and Drug Administration

5:00 PM – 6:30 PM  
**SCT Program Committee Meeting**

6:30 PM – 8:00 PM  
**Full Conference Reception**
Tuesday, May 17, 2011

7:00 AM – 5:00 PM  Registration

8:00 AM – 5:00 PM  Exhibits, Posters

7:50 AM – 8:50 AM  **Contributed Paper Sessions II**

**Moderator:** Simon Day

**Session 2A: Ethical Issues in Cluster Trials**

7:50 AM  31  Researchers’ Perceptions of Ethical Challenges of Cluster Randomized Trials: A Qualitative Analysis; Andrew McRae, University of Calgary

8:05 AM  32  Investigator Experiences with the Ethics Review Process of Cluster Randomized Trials: An International Survey; Shazia Chaudhry, Ottawa Hospital Research Institute

8:20 AM  33  Reporting of Research Ethics Review and Informed Consent Practices in Cluster Randomized Trials; Monica Taljaard, Ottawa Hospital Research Institute

8:35 AM  34  Factors Associated with Reporting of Patient Consent in Healthcare Cluster Randomized Trials; Andrew McRae, University of Calgary

**Session 2B: Ethical, Regulatory, Policy Issues**

**Moderator:** Nicole Close

7:50 AM  35  The Lack of Representativeness of Patients in Randomized Trials Endanger the Scientific Basis of Evidence-based Medicine; Joerg Hasford, University of Munich

8:05 AM  36  Open Versus Closed Access to Full Academic Trial Protocols: Advantages and Disadvantages; Sue Ross, University of Calgary

8:20 AM  37  Animals, Humans, and the Continuity of Evidence: Design and Preliminary Results of a Systematic Study of Clinical Translation; Jonathan Kimmelman, McGill University

8:35 AM  38  HIV PrEP: A New Tool for Prevention, Harm-Reduction or Harm-Potentiation? Madzouka B. Kokolo, Ottawa Hospital Research Institute

**Session 2C: HIV Design Issues**

**Moderator:** Jonathan Cook

7:50 AM  39  Metrics for Evaluating Surrogate Endpoints with Application to HIV Prevention Trials; James Dai, Fred Hutchinson Cancer Research Center

8:05 AM  40  Capitalizing Upon Local Capacity and Experience for Clinical Research Data Management in Resource Limiting Settings: The Kericho CLADE Study; Peter Yegon, Kenya Medical Research Institute/Walter Reed Project

8:20 AM  41  The Cameroon Mobile Phone SMS (CAMPS) Trial: the Protocol for a Randomized Controlled Trial of Mobile Phone Text Messaging Versus Usual Care for Improving Adherence to HAART; Lehana Thabane, McMaster University

8:35 AM  42  HIV Treatment Programs and Clinical Research in East Africa: A Symbiotic Relationship; Milton Omondi, Walter Reed Project Kenya, Kisumu-West, Kenya
Tuesday, May 17, 2011

Session 2D: Patient Recruitment, Enrollment, and Retention
Moderator: Alison McDonald
7:50 AM 43 Importance of Conference Calls for Coordinators in Multi-Center Clinical Trials; Laura Tipton, The George Washington University
8:05 AM 44 Can Patient Decision Aids Help Trial Participants? A New Approach to Informed Consent for Clinical Research; Jamie Brehaut, Ottawa Hospital Research Institute
8:20 AM 45 Multiple Mechanisms to Retain Participants in a Long-Term Randomized Clinical Trial: The Carotid Revascularization Endarterectomy vs. Stenting Trial; Mary Longbottom, Mayo Clinic
8:35 AM 46 Efficiency in Opening New Clinical Trials Versus Efficiency in Accruals; Yelena Novik, NYU Cancer Institute

Session 2E: Quality Assurance, and Monitoring
Moderator: Domenic Reda
7:50 AM 47 High Quality Risk Management for Clinical Trials: Use the Data at Your Hands to Manage Risk in Your Clinical Trials; Jochen Dress, Clinical Trial Center Cologne (BMBF Grant 01KN0706)
8:05 AM 48 Active Monitoring of Patient Recruitment in Surgical Trials; Inga Rossion, Study Center of the German Surgical Society
8:20 AM 49 An Examination of Site Visit Data Audit Results Compiled During the Initial Four Years of a Long-Term Clinical Trial; Wendy McBee, The EMMES Corporation
8:35 AM 50 Systematic Review of the Methods and Effects of Source Data Verification in Clinical Research; Roxanne Ward, Children’s Hospital of Eastern Ontario Research Institute

9:00 AM – 10:30 AM Invited Session 11
Design, Analysis and Monitoring of Clinical Trials: What if No Cox Model?
The Cox proportional hazards model has been used widely in design, analysis and monitoring of clinical trials for censored time-to-event endpoints. For many clinical trials, however, the assumption of proportionality between hazard functions over time, i.e., short-term effect being predictive of long-term effect, is not always practically feasible. In this session, we intend to invite three lead researchers from academia, industry and government to present their perspectives on the challenges and possible solutions when nonproportional hazards are expected.

Organizer and Chair: Ying Qing Chen, Fred Hutchinson Cancer Research Center
Speakers: Deborah Donnell, Fred Hutchinson Cancer Research Center — Interim monitoring when comparing short and long term strategies for prevention of HIV
Song Yang, National Heart, Lung, and Blood Institute, National Institutes of Health and Ross Prentice, Fred Hutchinson Cancer Research Center — Confidence procedures for the hazard ratio function
Zhigang Zhang, Memorial Sloan-Kettering Cancer Center

9:00 AM – 10:30 AM Invited Session 12
U.S. Government-funded Clinical Trials in the European Union: Challenges and Lessons Learned
Over the past decade, the United States (U.S.) National Institute of Allergy and Infectious Diseases has dramatically increased funding of international activities to promote worldwide health improvements. These international collaborations are particularly important for the successful completion of large clinical trials that could have
significant public health impact. The European Union (E.U.) Directive for Clinical Trials implemented by member countries in 2004 sets standards for drug manufacturers, ethics committees, sponsors and other parties involved in clinical trials of medicinal products. Unfortunately, some of these standards – or the interpretation of these standards by member countries – conflict with U.S. regulations or law. This presentation will focus on issues generated from various HIV trials conducted in the E.U. over the past five years in the INSIGHT network (International Network for Strategic Initiatives in Global HIV). Attention in each topic will be given to the lessons learned, including the resources invested to overcome obstacles, and recommendations for resolving differences between U.S. and E.U. clinical trial regulations.

**Organizer and Chair:** Jorge Tavel, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health

**Speakers:** Jorge Tavel, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
Stephane Berghmans, European Science Foundation
Jesper Graup, Copenhagen HIV Programme
Sarah Meredith, United Kingdom Medicines Research Council Clinical Trials Unit
Mary Smolskis, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health

**9:00 AM – 10:30 AM Invited Session 13**
*Student Scholarship Presentations*

In this session, students will present the papers selected as finalists in the student scholarship program.

**Speakers:** Adaptive Design Modifications to the Sequential Parallel Comparison Design for Clinical Trials — Michael Y. Mi, Harvard Medical School, Health Sciences and Technology
Validating Data Merging in Longitudinal Studies and Joint Modeling of Merged Longitudinal Data — Fei Wang, University of Michigan, Department of Biostatistics
Group Sequential Monitoring with the Proportional Odds Model — Kenneth Wu, University of Washington at Seattle, Department of Biostatistics

**9:00 AM – 10:30 AM Invited Session 14**
*Complex Interventions; Methodological Considerations for Development and Evaluation*

Healthcare interventions can be placed along a continuum from simple to complex. Simple interventions can be developed and evaluated through a relatively linear, phased process whereas more complex interventions require different approaches. Complex interventions often require a more iterative approach to development and initial evaluation prior to definitive randomized trials. Complex intervention trials are often clustered and may use a variety of design features to enhance their informativeness. Further additional analyses of randomized trials to evaluate hypothesized mediators and moderators are often desirable. Reporting of trials of complex interventions is challenging, with critics claiming lack of replicability even from published trial protocols. Over the past decade, guidance from the UK Medical Research Council has triggered interest in the articulation of more distinctive and explicit methods for developing and evaluating complex interventions.

This session aims to consider the current state of the methodology of complex intervention development and evaluation. Speakers will discuss intervention complexity providing examples of: complex intervention development processes; evaluating the fidelity of intervention delivery; analytical issues in evaluations of complex interventions; and guidance on reporting. This will be followed by a panel discussion and general discussion.

**Organizer:** Jill Francis, University of Aberdeen

**Chair:** Marion Campbell, University of Aberdeen
Tuesday, May 17, 2011

Speakers: Jeremy Grimshaw, Ottawa Hospital Research Institute
Jill Francis, University of Aberdeen
Graeme MacLennan, University of Aberdeen

Discussants: Jeremy Grimshaw, Ottawa Hospital Research Institute
Graeme MacLennan, Marion Campbell, Jill Francis, University of Aberdeen

9:00 AM – 10:30 AM Invited Session 15
How Polypharmacy Distorts Trial Evidence in Older Adults

Increasing age is often associated with the presence of multiple chronic diseases in the same patient. This frequently results in polypharmacy, making the interpretation of both trial evidence and the implementation of clinical practice guidelines difficult. Almost half of all persons over 65 have three or more chronic conditions and about one-fifth have five or more. A systematic application of clinical practice guidelines to an older adult with 5 chronic diseases has been shown to generate a medication profile that would require the consumption of 19 separate doses taken at five different times. This raises the uncomfortable issue that dealing with the multiple morbidities an older adult frequently has can become a full-time job. Clinical trials tend to under-report adverse events, and a clinical trial of a single medication can ignore the “collateral damage” such as delirium and falls that can result when a number of individually effective medications are taken as an aggregate. This session will examine the impact of polypharmacy on the applicability of trial evidence in older adults, specifically addressing the following:

1. We will examine how clinical practice guidelines when applied in the aggregate result in intrusive medical care that may well detract from the quality of life of an older adult population.
2. We will examine the adverse effects of polypharmacy in older adults that are not often picked up by phase III clinical trials, such as falls, drug-induced parkinsonism, gastrointestinal bleeding and delirium.
3. We will suggest alternative end-points that might better reflect the desired balance between quality and quantity of life in the older adult population.
4. We will attempt to suggest new approaches to conducting pragmatic trials in older adults that better reflect “real world” settings.

Organizer: Kenneth M. Madden, University of British Columbia

Speakers: Kenneth M. Madden, University of British Columbia
David B. Hogan, University of Calgary
Tom Perry, University of British Columbia

10:30 AM – 11:00 AM Break/Exhibits/Poster Prime Time

11:00 AM – 12:30 PM Invited Session 16
Industry Statisticians: Part of the Problem, Part of the Solution or Innocent Bystanders in Peer-Reviewed Medical Literature?

Manuscripts describing the results of clinical trials have been criticized with respect to incompleteness, bias, and conflict of interest of authors. One important focus of the criticism has been on industry sponsorship and industry-related issues with reporting. Several initiatives have been undertaken to address this perceived problem. One initiative, by JAMA, has been a requirement for an independent analysis of industry sponsored trials. Issues regarding authorship have been approached with guidelines regarding definition of the basis for authorship and with proposals to list the activities of the various authors. Conclusions that bias is common in industry sponsored research have been based on the frequency with which published industry-sponsored trials are positive.

The industry statistician can be seen as part of a problem of biased reporting, part of the solution of ensuring comprehensive intended analysis and reporting, or neutral with respect to the issue of what appears in publications. In this session, speakers will represent different perspectives from which the medical literature is approached:
The CONSORT statement is intended to provide direction in reporting clinical trial methods and results. A leader of the effort in developing CONSORT guidelines will comment on the objectives of the initiative and the performance of the initiative with respect to reducing biases in reporting clinical trial results.

A statistician with experience in both industry-sponsored and government sponsored clinical trials will critically review editors’ initiatives, peer review, and other options such as un-reviewed reporting of results at clinical trials registry sites.

A leader in evidence based medicine and clinical epidemiology will address the perception and the reality of industry-sponsored research as reported in the medical literature.

An industry statistician will present the perspective of the designer of the trial who monitored its implementation and planned its analysis. His stance is that these efforts lead the industry statistician to analyze and report the results scientifically without bias.

An FDA perspective on cases where the published results were not the same as submitted results will be presented.

Organizer: David Hall, Boehringer Ingelheim Pharmaceuticals
Speakers: David Moher, Ottawa Hospital Research Institute
          Janet Wittes, Statistics Collaborative, Inc.
          David Sackett, Kilgore Trout Research & Education Centre
          David Hall, Boehringer Ingelheim Pharmaceuticals
          Robert Temple, U.S. Food and Drug Administration

11:00 AM – 12:30 PM Invited Session 17
The Legal System: Evidence-Based Medicine’s Last Stand?

Randomized controlled clinical trials (RCTs) are the gold standard for determining efficacy and effectiveness in modern drug therapy. Regulatory bodies, physicians, and researchers rely on RCTs to make drug therapy decisions. But what if the apparent results from RCTs do not reflect the real evidence? What if important negative results are inaccurately reported or never even published? And what if a pharmaceutical manufacturer’s profit motive guides these publication decisions? Can physicians, medical researchers, and policy makers ever look beyond the biomedical literature to get to the truth about the drugs we use every day?

This presentation discusses how the legal system—specifically private litigation—can uncover the real results of RCTs. We will describe the decade-long legal saga of gabapentin (Neurontin), which culminated in 2010 with a federal jury in Boston finding that the manufacturer of gabapentin had engaged in fraud and racketeering by withholding or deceptively publishing results of RCTs while marketing the drug. The jury ordered the manufacturer to pay $142 million to a private insurer. The gabapentin case study is an important example of how litigation can expose unpublished or selectively published data. When physicians, researchers, and peer reviewers cannot access underlying data, the courts can unearth the real evidence.

We will also review briefly how other lawsuits and government investigations in the United States have elucidated the relationships between pharmaceutical manufacturers, academic medicine, medical journals, and medical education. Can the historical enmity between doctors and lawyers be transformed into an alliance for truly evidence-based medicine?

Speakers: Ilyas J. Rona, Greene LLP
          Palko S. Goldman, Greene LLP

11:00 AM – 12:30 PM Invited Session 18
Ethical Issues in Cluster Randomized Trials: Challenges and Preferred Solutions

Cluster randomized trials (CRTs) raise challenging ethical issues which have not yet been addressed adequately. As part of a Canadian Institutes of Health Research funded project seeking to develop international guidelines,
key areas of controversy will be introduced and preferred solutions will be proposed. Each talk will be followed by a guided discussion with members of the audience. The first talk will address the challenges of identifying who should be considered research subjects in a CRT, and from whom, how, and when informed consent should be obtained. Discussion will include applications in knowledge translation CRTs which commonly intervene on healthcare providers but measure outcomes on patients, as well as public health or health promotion trials in which interventions are applied at the level of the community. The second talk will address the relevance of clinical equipoise in CRTs and the ethical analysis of benefits and harms. Discussion will include challenges arising from the distinction between therapeutic and non-therapeutic procedures in trials involving a cluster level intervention, and between subjects who receive a target intervention and those who simply contribute data.

Organizer and Chair: Monica Taljaard, Ottawa Hospital

Speakers:
Jeremy Grimshaw, Ottawa Hospital Research Institute — Introduction
Andrew McRae, University of Western Ontario — Who is a Research Subject, and Informed Consent Issues in CRTs
Charles Weijer, University of Western Ontario — Clinical Equipoise and Benefit/Harm Issues in CRTs

11:00 AM – 12:30 PM Invited Session 19
The CATT Study: A Milestone in Comparative Effectiveness Research

Developing and conducting a clinical trial to compare the effectiveness of available treatments in a given disease is challenging; when the cost differential is very high, only one drug is FDA-approved for the indication, and the drugs are made by the same company, the challenges are multiplied many times over. This session will describe the saga of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT): Lucentis-Avastin Trial with emphasis on the issues that likely will be common to other clinical trials. Study enrollment began in 2008, two years after ranibizumab (Lucentis™) was approved by the FDA for age-related macular degeneration (AMD), and was completed in 2009. Ranibizumab is very closely related to bevacizumab (Avastin™), which was approved for several cancer indications beginning in 2004 and was being widely used off-label for AMD at the time ranibizumab was approved. Bevacizumab can be obtained for approximately one fortieth the cost of ranibizumab; however, it was critical to know whether the less expensive drug worked as well in preventing blindness as the more expensive drug and whether the safety profile was similar. Extensive negotiations among the National Institutes of Health, the Center for Medicare and Medicaid Services and the investigators, with input from the Food and Drug Administration, were necessary to develop a pathway to support and conduct this important study. Roadblocks, many still existing, will be discussed.

Organizer and Chair: Susan S. Ellenberg, University of Pennsylvania School of Medicine

Speakers:
Maureen Maguire, University of Pennsylvania
Daniel Martin, Cleveland Clinic Foundation

Discussants:
Maryann Redford, National Eye Institute
James Rollins, Center for Medicare/Medicaid Services

11:00 AM – 12:30 PM Invited Session 20
Challenges in Infectious Disease Clinical Trials Conducted in India and Southeast Asia

There are many advantages of conducting clinical trials in Asia, including reduced cost, faster enrollment, and high-quality hospital infrastructure. Despite these benefits, many challenges remain. Studies that enroll patients in both the U.S. and Asia pose special challenges in terms of organization, ethics and biostatistics. Combining the experience of the F.I. Proctor Foundation at the University of California, San Francisco, The Bill and Melinda Gates Foundation, and Pfizer, Inc., this session will offer perspectives on clinical trials from inception, obtaining funding and regulatory approvals, trial coordination, and data management and analysis. These experts are involved in NIH-funded infectious eye trials in India, malaria trials in Burma and Thailand, and tuberculosis trials in South Asia. Issues specific to academic, industry and foundation-sponsored trials will be discussed.
Organizers: Nisha R. Acharya, F.I. Proctor Foundation, University of California
Thomas M. Lietman, F.I. Proctor Foundation, University of California

Speakers:
Nisha R. Acharya, F.I. Proctor Foundation, University of California — Why do Trials in South Asia?
Catherine Oldenburg, F.I. Proctor Foundation, University of California — Coordination from 10,000 Miles Away
Regina Rabinovich, Bill and Melinda Gates Foundation — Challenges with Conducting TB Trials in South Asia
Travis Porco, F.I. Proctor Foundation, University of California — Statistical Issues with Enrolling Patients in Asia and the U.S. in the Same Trial
Charles Knirsch, Pfizer Inc. — Design and Conduct of Phase 2 Malaria Trials in Southeast Asia

Discussants:
Marian Fisher
Nisha R. Acharya, F.I. Proctor Foundation, University of California
Tom Lietman
Catherine Oldenburg, F.I. Proctor Foundation, University of California
Peter Small
Travis Porco, F.I. Proctor Foundation, University of California
Charles Knirsch, Pfizer Inc.
Elizabeth Esterberg

12:30 PM – 1:50 PM Lunch/SCT Business Meeting (Lunch included in Registration)

1:50 PM – 2:50 PM Contributed Paper Sessions III
Session 3A: Facilitating Research
Moderator: Wendy McBee

1:50 PM 51 Fostering Translational Research at an Academic Medical Center; Dorothee Arenz, University of Cologne
2:05 PM 52 An Organizational Structure to Manage Analyses and Manuscript Development in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial; Margaret Bell, New England Research Institutes
2:20 PM 53 Project Managers are Worth Their Weight in Gold; Tilly Yau, EmpiriStat, Inc.
2:35 PM 54 The Delicate Balance between Independence and Collaboration: Perspectives from Academic and Industry Statisticians; Chao-Yin Chen, Amgen, Inc.

Session 3B: Methodological Issues in Trials
Moderator: Tim Ramsay

1:50 PM 55 Evaluation of Masking Success of Sham Ocular Injections; Adam Glassman, Jaeb Center for Health Research
2:05 PM 56 Blinding in Randomized Behavioral Clinical Trials; Elizabeth Avery, Rush University Medical Center
2:20 PM 57 Randomization and Random Allocation in Reader Diagnostic Studies; Patricia Feeney, Statistics Collaborative, Inc.
2:35 PM 58 When Should RCTS Standardize Co-Interventions?; Yuko Palesch, Medical University of South Carolina
Tuesday, May 17, 2011

Session 3C: Patient Safety
Moderator: Marion Campbell
1:50 PM 59 Suicide Risk in Substance Abuse Treatment Clinical Trials, Is Adverse Event Reporting Alone Sufficient?; Robert Lindblad, The EMMES Corp – 2011 Sylvan Green Award
2:05 PM 60 Adverse Event Signal Detection: Overall comparisons, Future Projections and False Discoveries; Jing Huang, Amgen Inc
2:20 PM 61 Risk of Death with Aprotinin in Cardiac surgery: A Bayesian Evidence Synthesis of Randomized and Observational Studies; Brian Hutton, McGill University
2:35 PM 62 A New Tool for Flagging Adverse Events of Potential Clinical Interest; Li Zhou, Axio Research LLC

Session 3D: Trial Design
Moderator: Susan Halabi
1:50 PM 63 Cluster Randomization of Test and Care Sites in the TLC-Plus Trial; Deborah Donnell, Fred Hutchinson Cancer Research Center
2:05 PM 64 Futility Trials in Neurology Revisited; Barbara Tilley, University of Texas, School of Public Health
2:20 PM 65 Outcome Choice in the design of Clinical Trials for the Elderly; Michael Miller, Wake Forest University School of Medicine
2:35 PM 66 The STAR Trial: Can Quality of Life Benefit Offset Any Survival Detriment?; Fiona Collinson, University of Leeds

Session 3E: Trial Monitoring
Moderator: Colin Begg
1:50 PM 67 Potential Dangers of Inappropriate Futility Boundaries; Susanne May, University of Washington
2:05 PM 68 Comparison of Futility Monitoring Methods Using RTOG Clinical Trials; Qiang Zhang, Radiation Therapy Oncology Group, American College of Radiology
2:20 PM 69 Calculating and Presenting Conditional Power at Interim Looks for an Adjudicated Time-to-Event Outcome; Susan Assmann, New England Research Institutes
2:35 PM 70 Issues Surrounding Interim Monitoring of a 3-Armed Clinical Trial: Experience from a Study of Oxytocin Regimes for Prevention of Bleeding after Vaginal Delivery; Jeff Szychowski, University of Alabama at Birmingham

2:50 PM – 3:20 PM Break/Exhibits/Poster Prime Time

3:20 PM – 4:50 PM Invited Session 21
Improving Safety Notifications to Investigators and Patients – Evolving Practice, Alternatives, and FDA Perspectives

This session will present the results of an original research project sponsored by the Clinical Trials Transformation Initiative (CTTI) and conducted collaboratively with FDA, academic, and industry team members to improve safety reporting to IND investigators, including primary research, patient perspectives, and expert panel conclusions; the implications of the new FDA premarket safety reporting requirements in this context will also be explored.
This session will have 3 parts covering interrelated facets of clinical trial safety reporting to investigators and patients—an evolving critical issue. Each part presents original information produced in collaborative efforts by FDA, academia and industry teams. Together they offer a complete perspective on legislation, current practice and future directions.

- **Part 1 Original Research-CTTI Safety Project** – The Clinical Trials Transformation Initiative (CTTI), a public-private partnership founded by FDA & Duke University, oversees a collaboration of over 50 stakeholders of government, academia, industry, and patient groups. CTTI identifies practices that increase the quality and efficiency of clinical trials. This part of the session will present the results of a 2009 project (“Improving the System of Reporting Unexpected SAEs to IND Investigators”), which generated empirical evidence of current systems and will suggest improvements to inform investigators and optimize patient protection. Academic, FDA and industry project team members conducted primary survey research of 3 populations (sponsors, investigators, and patients) to elucidate: 1) current sponsor practices, 2) investigator time and perceived value, 3) a comparison of alternative models, and 4) patient perspectives of IND safety notifications.

- **Part 2 FDA IND Safety Reporting Requirements and Perspectives** – This part will first present the FDA perspective on issues seen with prior IND safety reporting regulations and how implementation impacts the number and value of safety reports that investigators receive. Second, the FDA’s new final rule for “Premarketing Safety Reporting for Human Drug and Biological Products” (released September 2010) will be reviewed, and intent and implications to increase report quality, advance worldwide consistency, and strengthen safety monitoring will be discussed.

- **Part 3 Expert Panel Proceedings** – The CTTI project concludes in October 2010 with a broad expert panel from academic, FDA, and industry organizations to review findings and develop recommendations for improving the quality and efficiency of reporting safety signals to clinical trial investigators. This part of the session will review the key issues and expert recommendations from that meeting that synthesize all of the preceding information.

  **Organizer:** Sundeep Sethi, Amgen Inc.
  **Speakers:**
  Robert M. Califf, Duke University
  Robert Temple, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
  Sundeep Sethi, Amgen Inc.

3:20 PM – 4:50 PM  **Invited Session 22**
**The Changing World of Data Management**

Technological progression has been shaping and redefining the responsibilities of and interactions with clinical data managers. Clinical data management has shifted from mere document processing to the information technology world of Internet data capture and remote data collection. Validation and consistency checks are now the responsibility of a sophisticated electronic data capture system requiring a data manager to understand software systems and how the software development lifecycle is maintained to ensure the integrity of data acquisition. The data manager role and responsibility requires a change in skill set and knowledge base to ensure an understanding of information technology, electronic data management structure, and system updates and compliance.

This session will discuss how and why data management is changing and what are the influencing factors to these changes. A discussion on the skill set a data manager should have to succeed in the changing field of data management. We will also present how IT staff and data managers should interact to efficiently perform the responsibilities assigned to each group.

  **Organizer:** Kristine Nelson, The EMMES Corporation
  **Chair:** Devin Hunt, EmpiriStat, Inc.
Invited Session 23
Frequentist, Bayesian and Likelihood designs for a Phase II Cancer Trial with a Time-
to-Event Endpoint: Head to Head Comparison of Three Philosophies of Trial Design

Three different study designs for a Phase II Cancer Trial – each from a different statistical paradigm – will be presented, compared and contrasted. This is similar in style to “critical assessment” approaches that have been used in recent years for assessment of microarray and protein data analysis (CAMDA and CASP, respectively). Here, given the same set of trial goals and parameters, three different designs are separately developed prior to the meeting and then presented together. Although there are clearly differences in how trials are designed using these three philosophical approaches, it is rare (if not non-existent) to fully consider three design approaches for the same clinical trial.

The parameters and specifics of the trial have been outlined in advance and presenters will propose a study design to represent their paradigm. The trial under consideration is a phase II cancer clinical trial with two treatment arms. The primary endpoint is progression-free survival (PFS) and a secondary endpoint is safety. Each treatment arm consists of standard therapy plus a new agent and it is ethical to randomize between arms. Presenters have been encouraged to incorporate adaptive stopping rules and adaptive randomization, futility analyses, safety looks, etc. and to develop a flexible and efficient study design. Designs will be compared based on their operating characteristics, uniqueness, practicability, efficiency, and expected sample size. Each presenter will have an equal amount of time to present his trial, and the discussant will also get the same amount of time to comment on the similarities and differences, strengths and weaknesses. There will also be time allowed at the end of the session for questions and discussion.

Organizers: Elizabeth Garrett-Mayer
Jeffrey Blume

Moderator: Elizabeth Garrett-Mayer

Speakers: Jeffrey Blume — Likelihood
Scott Berry — Bayesian
Stephen George — Frequentist

Discussant: Susan Ellenberg

Invited Session 24
Practical Application of Adaptive Treatment Strategies in Trial Design and Analysis

Adaptive treatment strategies are sequences of treatments that are individualized based on certain patient outcomes. In practice, that is what healthcare providers do. For example, they start with Treatment A, and if the patient’s condition does not improve within some number of days by some quantifiable measure, the healthcare provider switches to Treatment B. This is an adaptive treatment strategy. Now healthcare providers may ask: what is the best treatment strategy for treating a certain condition? One way to address this question is via Sequential Multiple Assignment Randomized Trials (SMARTs), which are clinical trials with multiple stages of treatment, where participants are re-randomized at each stage based on intermediate outcomes. These trials in fact compare adaptive treatment strategies. Their results may indeed have more practical applications than simply comparing Treatment A to Treatment B.

The goal of this session is to describe SMART designs, and illustrate from both a statistician’s and a clinical researcher’s perspective how the research that has been conducted so far on SMART designs is applied to
simple as well as complex clinical trials. The speakers will also discuss the challenges they faced in running SMART studies, and how they dealt with those challenges.

Just to be clear, this session is not about adaptive designs. Adaptive designs are changes made to the trial design after taking a look at aggregated data, whereas SMART designs involve decisions made at the participant level.

Organizer & Chair: Paul Wakim, National Institute on Drug Abuse, National Institutes of Health

Speakers: Susan Murphy, University of Michigan
          Kevin Lynch, University of Pennsylvania
          James McKay, University of Pennsylvania

3:20 PM – 4:50 PM  Invited Session 25
New Insights in Reporting Clinical Trials: From Protocol to Systematic Review and Beyond

Use of reporting guidelines is associated with improved quality of reporting clinical research. The CONSORT Statement, a reporting guideline for randomized trials, is widely recognized; it is endorsed by more than 600 medical journals and editorial groups globally yet there are shortcomings in how they have implemented it. Reporting trials is one step on the continuum of clinical trials. Other steps include developing and reporting trial protocols and understanding the harmful effects of including inadequately reported clinical trials in systematic reviews. Related issues include whether and how clinical trial data can be shared. This session will present the new SPIRIT 2010 Statement (Chan), a reporting guideline for protocols of randomized trials, an update on CONSORT 2010 (Altman), new strategies for journals wanting to endorse and implement CONSORT (Moher), and some problems associated with including inadequately reported trials in systematic reviews (Altman). The session will end with an in-depth discussion about data sharing (Hrynaszkiewicz).

Organizers: David Moher
             Doug Altman

Speakers: Iain Hrynaszkiewicz
          An-Wen Chan

5:00 PM – 6:20 PM  Plenary Session: Trial of the Year/Project ImpACT

This session will open with two historic trials from the ImpACT data bank (of “Important Achievements in Clinical Trials”) that generated both great light (illuminating the science of RCTs and the practice of medicine) and considerable heat (as sacred cows went up in smoke).

The session will then present the award for the SCT/ImpACT Trial of the Year for 2011.

Co-Chairs and Speakers: Steve Goodman, Johns Hopkins University
                         Dave Sackett, Trout Research Centre

6:30 PM – 7:30 PM  Affinity Group Receptions:
Information Technology – Plaza B (2nd Floor)
Clinical Research Associates – Plaza C (2nd Floor)
MD Clinical Trialists – Georgia A (2nd Floor)
Members of Industry or FDA – Georgia B (2nd Floor)
Trialists Working in Europe – Regency A (3rd Floor)
Trialists Working in Asia – Regency B (3rd Floor)
### Thursday, May 18, 2011

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<th>Time</th>
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<tr>
<td>7:00 AM – 11:00 AM</td>
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<td>8:00 AM – 8:45 AM</td>
<td><strong>Founders Lecture – Johan Karlberg, MD, PhD, BSc</strong>&lt;br&gt;&lt;br&gt;Asian Clinical Trial Trends, By Type of Sponsor, Trial Phase, Disease Area, and Country</td>
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| 9:00 AM – 10:30 AM| **Contributed Paper Sessions IV**<br><br>**Session 4A: Clinical Epidemiology**<br><br>*Moderator: Monica Taljaard*
  - 9:00 AM 71 Effect of Celecoxib on Adenoma Count in a Randomized Trial of Celecoxib for the Prevention of Sporadic Colorectal Adenoma using a Zero-inflated Poisson (ZIP) Model with Random Effects; Meier Hsu, Memorial Sloan-Kettering Cancer Center
  - 9:15 AM 72 The Challenges of Facilitating and Supporting the Efficient and Secure Exchange of Data in a Multi-Site Cooperative Group that is Funded by Government and Industry; Scott Gould, Gynecologic Oncology Group Statistical & Data Center
  - 9:30 AM 73 Laparoscopic and Open Colorectal Cancer Surgery: An Overview of Systematic Reviews; Guillaume Martel, The Ottawa Hospital, University of Ottawa
  - 9:45 AM 74 Difficulties in Running a Randomized Controlled Trial in the Real World of Social Interventions in Denmark; Maiken Pontoppidan, SFI the Danish National Center for Social Research
  - 10:00 AM 75 How Did We Get Here from There? Experiences from N0147: A North Central Cancer Treatment Group (NCCTG) Phase III Randomized Clinical Trial; Michelle Mahoney, Mayo Clinic
  - 10:15 AM 76 Explaining Treatment-by-Site Interaction in Multisite Clinical Trials: An Application to the TORDIA Clinical Trial; Kaleab Abebe, University of Pittsburgh

**Session 4B: Hot Topics in Conducting Trials**<br><br>*Moderator: Wendy Parulekar*
  - 9:00 AM 77 Clinical Trial Registries - Where Do We Stand?; Gabriele Dreier, University Medical Center Freiburg
  - 9:15 AM 78 Did the Extension of CONSORT to Cluster Randomized Trials Result in Improved Quality of Reporting and Study Methodology?; Noah Ivers, University of Toronto
  - 9:30 AM 79 The Influence on CONSORT on the Quality of RCTs: An Updated Review; David Moher, Ottawa Hospital Research Institute
  - 9:45 AM 80 The Durability of Vaccine Efficacy on the Incidence of Herpes Zoster Afforded by ZOSTAVAX; Xiaoming Li, Merck Research Laboratories
  - 10:00 AM 81 Lean Sigma in the New Health Landscape: An Application in Biostatistics; Josephine Measusres, Quintiles
  - 10:15 AM 82 The National Institute of Neurological Disorders and Stroke Clinical Research Collaboration (NINDS CRC); Summary of Pilot Activities; Anne Lindblad, The EMMES Corporation
Wednesday, May 18, 2011

Session 4C: Outcome Assessment Issues

**Moderator:** Ivan S.F. Chan

- **9:00 AM 83** Predictors of All-causes Mortality on 6975 Patients of the GISSI-HF Trial on Heart Failure; Simona Barlera, Istituto di Ricerche Farmacologiche Mario Negri
- **9:15 AM 84** Imputation of Survival Outcomes in Clinical Trials: Risk-stratified Imputation in Informative Censoring; George Howard, University of Alabama at Birmingham
- **9:30 AM 85** Ascertaining Dementia Related Outcomes for Deceased or Proxy-Dependent Participants: An Overview of Whims Supplemental Case Ascertainment Protocol (SCAP); Sarah Gaussoin, Wake Forest University School of Medicine
- **9:45 AM 86** Comparison of Adjudicated Events to Initial Clinic Event Reporting in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial; Laura Lovato, Wake Forest University School of Medicine
- **10:00 AM 87** Methods for Choosing a Cut Point when Dichotomizing a Continuous Response - a Case Study of Predicting Infant Survival with High Resolution Melting score; Lei Wang, Fred Hutchinson Cancer Research Center
- **10:15 AM 88** Time to Composite Outcomes with Semi-Competing Risk: A Comparison of Methods to Detect Treatment Heterogeneity within a Composite Outcome; Janice Pogue, McMaster University

Session 4D: Statistical Issues

**Moderator:** Tim Ramsay

- **9:00 AM 89** Estimation of Survival for All Treated Patients in the Randomized Discontinuation Trial Design; Theodore Karrison, University of Chicago
- **9:15 AM 90** Application of Excess Zero Methodology to Oral Health-Related Quality of Life: PEARL Network Findings; Abigail Matthews, The EMMES Corporation
- **9:30 AM 91** The Impact of Association Between Endpoints on Performance in Seamless Phase II/III Clinical Trial Designs; Meihua Wang, Radiation Therapy Oncology Group
- **9:45 AM 92** Robust Inference via Permutation Distributions; Jitendra Ganju, Amgen, Inc.
- **10:00 AM 93** Analysis of Incomplete Non-Normal Longitudinal Lipid Data; Jiajun Liu, Merck Research Lab
- **10:15 AM 94** Regression with Latent Variables: A Better Way to Analyze Composite Scores from Instruments for Subjective Outcomes in Clinical Trials; Chengwu Yang, College of Medicine, Pennsylvania State University

Session 4E: Trial Designs

**Moderator:** Dean Fergusson

- **9:00 AM 95** Adaptive Design for Clinical Trials: Perspectives from a Workshop; Christopher Coffey, University of Iowa
- **9:15 AM 96** A Biomarker-Based Adaptive Two-stage Randomized Phase II Study Design; Virginia Filiaci, Gynecologic Oncology Group Statistical and Data Center
Wednesday, May 18, 2011

9:30 AM 97 Sequential Randomized Phase II Clinical Trial; Xiaomin Lu, University of Florida
9:45 AM 98 Efficient Design and Analysis of Clinical Value for Paired Medical Tests at Single and Serial Time Points; Timothy Chang, University of Wisconsin-Madison
10:00 AM 99 Guidance Manual for Phase II Trial Design in Cancer; Sarah Brown, University of Leeds
10:15 AM 100 Challenges in the Design and Analysis of Non-Inferiority Trials: A Case Study; Valerie Durkalski, Medical University of South Carolina

10:30 AM – 10:45 AM Break

10:45 AM – 12:15 PM Invited Session 26
Harmonizing the Human-Computer System Relationship to Optimize Trial Operation Management in the Era of Web-based CTMS

Web-based Clinical Trial Management Systems (CTMS) are becoming the standard tool for today’s large multi-center clinical trials. While providing secure and efficient functionality for many aspects of trial operation management, a generic standardized installation of CTMS may also conflict with the dynamic and specific demands of different trials, creating resistance from the end users which could negatively impact trial conduct. In this session, we discuss the importance of the human’s role and the limitation of the computer system in trial operation management, and strategies for harmonizing the human-computer system relationship. Speakers will address these issues from different points of views, including data and project managers at trial coordination centers, clinical investigators and study coordinators at clinical sites, as well as computer system developers.

Organizer and Chair: Wenle Zhao, Medical University of South Carolina

Speakers: Catherine Dillon and Bonnie Waldman, Medical University of South Carolina – Roles of the Data Manager and Project Manager in the Optimization of Large Multi-center Trial Operation Management in Web-based CTMS Era
David Wright, Emory University — User’s Involvement in the Optimization of Computerized Trial Management System
Wenle Zhao, PhD, Medical University of South Carolina – Flexibility – the Key to a Successful CTMS

Discussant: Kristine Nelson, The EMMES Corporation

10:45 AM – 12:15 PM Invited Session 27
Update on Results from the Clinical Trials Transformation Initiative

At SCT’s 2010 annual meeting, leaders from the Clinical Trials Transformation Initiative (CTTI) described their organization’s approach to improve the quality and efficiency of clinical trials. Created as a public–private partnership, CTTI is generating empirical evidence about current practices in the conduct of clinical trials and using its broad stakeholder involvement to identify, understand, and propose removal or alteration of those activities that do not contribute to the quality or reliability of data or patient protections.

Two of CTTI’s projects have now completed all of their component efforts, and a summary of their findings will be reported in this session. These projects include one that focused on clinical trial oversight (i.e., monitoring) and one that addressed reporting to investigators of serious and unexpected suspected adverse reactions and subsequent communication to patients.

A new CTTI project is intended to create a reliable method to track trends in the conduct of clinical trials over time. Specifically, CTTI is seeking to improve the public interface for use of aggregate data from the ClinicalTrials.gov database. As it is currently configured, ClinicalTrials.gov is optimized for transactions regarding individual
trials. The entire dataset, however, is difficult for naïve users to evaluate in an aggregate fashion. CTI therefore has undertaken to make the acquisition and use of aggregate data from ClinicalTrials.gov more user-friendly for analysis, which will also enable the production of a valid snapshot of the clinical trial system’s functionality at any point in time.

This session will feature leaders from these three CTI projects, each describing their activities, results, and recommendations. A representative from the U.S. Food and Drug Administration will also provide a regulatory perspective on the CTI findings and recommendations.

**Organizer:** Judith M. Kramer, Duke Translational Medicine Institute

**Speakers:**
- Robert M. Califf, Duke University
- Briggs W. Morrison, Pfizer, Inc.
- Sundeep Sethi, Amgen, Inc.
- Robert Temple, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

**10:45 AM – 12:15 PM** **Invited Session 28**

**New Developments/Emerging Issues in Early Phase Adaptive Clinical Trial Design with Application or Implication in Current or Future Clinical Trials in Asia**

While novel statistical designs for early phase clinical trials are nowadays more frequently adopted in practice in North America and other western countries, they have not been equally widely applied in Asia. This may have prevented more efficient, ethical, and scientifically sound clinical trials being designed and conducted in Asia. Furthermore, new issues have risen in the design of clinical trials in Asia. This session focuses on these new developments and emerging issues. Two talks will be given by researchers from Asia and one by a researcher from the US whose topic has important implication in designing and conducting future oncology trials in Asia. All three speakers and the discussant are statisticians.

**Organizer:** Yisheng Li, University of Texas M.D. Anderson Cancer Center

**Chair:** TBD

**Speakers:**
- Satoshi Morita, Yokohama City University Medical Center — Sequential Dose-Finding in Phase I Clinical Trials in Japan
- Xuelin Huang, University of Texas M.D. Anderson Cancer Center — Using Information on Both Short-Term Response and Long-Term Survival in the Design of Future Oncology Clinical Trials in Asia
- Guosheng Yin, The University of Hong Kong — Two-stage Dose-Finding for Cytostatic Agents in Phase I Clinical Trials

**Discussant:** Rick Chappell, University of Wisconsin-Madison

**10:45 AM – 12:15 PM** **Invited Session 29**

**Assessing Biosimilarity of Follow-on Biologics**

As more and more biological products going off patent, it is a concern whether the generic versions of the innovative biologic products, which are referred to as follow-on biologics by the United States Food and Drug Administration (FDA) or biosimilars by the European Medicines Agency (EMA), are therapeutically equivalent to the innovative biologic products and whether they can be used interchangeably. Unlike the small molecule drug products, biological products are derived from living cells. As a consequence, there are fundamental differences between small molecule drug products and biologic products in terms of mechanism of action, structure, biological activity, pharmacokinetics and pharmacodynamics, and manufacturing process. Thus, standard criteria and methods for assessment of bioequivalence for drug products are not applicable to the biologic products.
Currently there is no established regulatory pathway for approval of follow-on biologics. However, there were a handful of individual submissions reviewed by the FDA in the last few years. From these reviews, Woodcock et al. (2007) pointed out that for assessment of similarity of follow-on biologics, the FDA would consider the following factors regarding (1) the robustness of the manufacturing process, (2) the degree to which structural similarity could be assessed, (3) the extent to which mechanism of action was understood, (4) the existence of valid, mechanistically related pharmacodynamic assays, (5) comparative pharmacokinetics, (6) comparative immunogenicity, (7) the amount of clinical data available, and (8) the extent of experience with the original product.

In this invited session, we will focus on the scientific/statistical issues surrounding the assessment of follow-on biologics including quality, pharmacokinetics and pharmacodynamics, clinical efficacy and safety and drug interchangeability, and how regulatory agencies and industry are evolving to deal with these issues.

Organizer: Shein-Chung Chow, Duke University School of Medicine
Chair: Peter Lachenbruch, Oregon State University
Speakers:
- Yun Chon, Amgen, Inc. – Assessing Follow-on Biologics in Rheumatoid Arthritis
- Laszlo Endrenyi, University of Toronto — Determination of the Similarity of Follow-on Biologics
- Eric Chi, Amgen, Inc. — Some Possible Study Designs to Assess Biosimilarity and Interchangeability for Follow-on Biologics
Discussant: Shein-Chung Chow, Duke University School of Medicine

10:45 AM – 12:15 PM Invited Session 30
Evolving Role of Data Safety Monitoring Board Members for Oncology Trials in the 21st Century

Traditionally the primary roles of the Data Safety Monitoring Boards (DSMBs) have been to ensure overall safety of trial participants, monitor trial progress, and also to make sure that the trials are conducted ethically and scientifically rigorously. However, given the high rate of failure seen in many late stage advanced oncology studies, the questions arises whether the DSMB, by virtue of having access to un-blinded data, need to and should do more in order to take corrective actions that would salvage a clinical trial that would have otherwise “failed”. For instance, evolving scientific information (either external or internal to the trial) may suggest that patients with certain biomarkers may benefit from the investigational agent(s) whereas the complimentary group does not. In such a situation, can the trial design be modified to continue with the targeted population? Another common situation encountered is that the interim data may suggest that the actual treatment benefit, although still clinically meaningful, is smaller than the hypothesized treatment benefit and an appropriately re-sized study may have a better chance of demonstrating this benefit. While statistical methodologies have been developed to minimize some of the biases likely to arise due to making such mid-stream changes, questions remain on how to minimize operational biases that are not easily quantifiable. Such operational biases, either real or perceived, can seriously jeopardize the validity of a trial if not adequately controlled by an independent group of advisors without any vested interest in the trial outcome. A well appointed DSMB may be in an unique position to advise the sponsor and keep the health authorities engaged so valuable resources can be saved in bringing a potentially life-saving product to patients.

Organizer: Pabak Mukhopadhyay, Novartis Pharmaceuticals Corporation
Chair: Bo Yang, Merck Research Laboratories
Speakers:
- Janet Wittes, Statistics Collaborative, Inc.
- Thomas Gwise, U.S. Food and Drug Administration
- Ram Suresh, Merck Research Laboratories
Poster Presentations

Order of Poster Presentations is subject to change – Please consult final program

Poster Presentation Monday, May 16, 2011, 8:30 AM – 5:00 PM
Prime Time 10:00 AM – 10:30 AM and 3:00 PM – 3:30 PM

P01 Estimating Clinic Staff Time for Patient Visits in the Accord Trial; Laney Light, Wake Forest University School of Medicine

P02 Evaluation of Imbalance in Stratified Blocked Randomization by Investigating Validity of Hallstrom & Davies Models; Guenther Kundt, University of Rostock

P03 Monitoring Therapy Sessions for Adherence to Protocol; Theresa Sax, University of Pittsburgh- Graduate School of Public Health

P04 Program in R to Calculate Adherence with Medication Regimen; Robert Edson, VA Cooperative Studies Program Coordinating Center, Palo Alto, CA

P05 A Complex Web-based Structure for Coordinating Review and Tracking Progress of Ancillary Studies in the National Lung Screening Trial; Jennifer Rosenbaum, Westat

P06 Monitoring the Progress of Clinical Trials in a Network Setting: Experience from the National Drug Abuse Treatment Clinical Trials Network; Paul VanVeldhuisen, The EMMES Corporation

P07 Experiences of Delivering a Practice-based Randomized Controlled Trial; Clare Jones, The University of Manchester

P08 Challenges and Lessons Learned in a Cluster Randomized Trial in the Community; Martina Mueller, Medical University of South Carolina

P09 Incorporating the Curation of Metadata in a Dental Practice-Based Research Network; Sherita Ala’i, The EMMES Corporation

P10 The Parkinson’s Progression Markers Initiative: A Prospective Biomarkers Study; Christopher Coffey, The University of Iowa

P11 Efficient Management of Diversified Funding within the Gynecologic Oncology Group (GOG) Statistical and Data Center (SDC); Sally Bialy, Gynecologic Oncology Group

P12 Risk Ratio Verse Odds Ratio in Clinical Trials of Binary Outcomes; Kellee Miller, Jaeb Center for Health Research

P13 Testing Lipid Treatment Effects in the Presence of Skewed Data Caused by Off-Therapy Discontinuation Values; Aditi Sapre, Merck & Co

P14 Event Adjudication of Visual Field Endpoints in The Ocular Hypertension Treatment Study (OHTS); Mae Gordon, Washington University School of Medicine

P15 Supplementing the OnCore Clinical Research Management System with a Web-Based Blinded Randomization Module for Investigator Initiated Oncology Trials; Brent Shelton, University of Kentucky

P16 Achieving Complete and Clean Data in Preparation for Data Analysis; Sunny Chan, Sunnybrook Research Institute

P17 Processes Implemented to Ensure Successful Follow-Up During Ongoing Recruitment; Kathryn Mangoff, Sunnybrook Research Institute

P18 The Lifestyle Interventions and Independence for Elders (LIFE) Intervention Tracking System: Monitoring Treatment Fidelity and Promoting Behavior Change; W. Jack Rejeski, Wake Forest University

P19 Missing Covariate Data with a Survival Endpoint: Problems and Solutions Pertaining to Design, Data Collections and Analysis; Donna Levy, Rho, Inc.

P20 Randomization Issues in a Randomized Multi-center Trial of an Educational Intervention for Improving Glucose Control in Patients with Diabetic Retinopathy; Bambi Arnold, Jaeb Center for Health Research

P21 Methods in Promoting a Clinical Research Trial; Dalah Mason, Sunnybrook Research Institute

P22 Unmasking Patients While Minimizing Bias in Future Follow-up Studies; Mariam Saleem, Sunnybrook Research Institute
Poster Presentations

Order of Poster Presentations is subject to change – Please consult final program

Poster Presentation Monday, May 16, 2011, 8:00 AM – 5:30 PM
Prime Time 10:00 AM – 10:30 AM and 3:00 PM – 3:30 PM

P23 Strategies Implemented to Achieve the Follow-up Goal in a 5-Year Follow-up Study; Mariam Saleem, Sunnybrook Research Institute

P24 The Impact of Substantial Case Report Form Modifications Post Database Launch in a Multi-Center Data Registry; Danielle Johnson, The EMMES Corporation

P25 Making Meeting Scheduling More Efficient, Simple, and Reliable: Using KAI’s Web-based Shared Calendar Application; Ben Piper, KAI Research, Inc., an Altarum Company

P26 Creating a Digital Library for Gynecologic Oncology Group (GOG) Manuscripts Utilizing the Statistical and Data Center (SDC) Information Technology Infrastructure (SDC); Melissa Leventhal, Gynecologic Oncology Group

P27 Description of the Implementation and Execution of the Secondary Prevention of Small Subcortical Strokes Study (SPS3) Promoted by the NIH in Spain; Ariadna Martin, Hospital Universitario de Bellvitge

P28 Twenty Four Month Outcomes of Randomized Equivalence Trial of Two Surgical Techniques for Women with Stress Urinary Incontinence: Retropubic and Transobturator Midurethral Slings (TOMUS); Heather Litman, New England Research Institutes

P29 An Assessment of Different Methods for Calculating Confidence Intervals on Proportions; Mark Schactman, Statistics Collaborative, Inc.

P30 The Benefits and Challenges of Utilizing a European CRO to Facilitate Master File Maintenance, Health Authority Submissions, and On-Site Monitoring for an International Clinical Trial; Traci Schwieger, The University of Iowa

P31 The Secondary Prevention of Small Subcortical Strokes Study Experience at International Sites; Ana Roldan, University of British Columbia

P32 Complexities of Conducting Substance Abuse Trials; Evan Hempel, KAI Research, Inc, an Altarum Company

P33 The Control of Hypertension in Pregnancy Study (CHIPS) Regional Collaborators’ Teleconferences – An Effective Approach to Regional Co-Ordination; Jennifer Menzies, The University of British Columbia

P34 Close Out Gets the Attention: But Who Turns on the Lights?; Fawna Start, EmpiriStat, Inc.

P35 Quality, Quantity and Inference: What Can We Learn From Hospitalization Endpoints?; Thomas Liz, Axio Research, LLC

P36 Incorporation of an Additional Interim Analysis During the Running of a Randomised Clinical Trial Using Group Sequential Design Methodology; Helen Marshall, University of Leeds

P37 The Challenges of Recruiting for an Ancillary Study Initiated after an Ongoing Clinical Trial; Letitia Perdue, Wake Forest University Health Sciences

P38 Resolve Problems and Errors - Corrective and Preventive Actions (CAPA) for Clinical Trials; Jochen Dress, Clinical Trial Center Cologne (BMBF Grant 01KN0706)

P39 Implementing Multiple BP Measurement Methods in an RCT: The Blood Pressure in Hemo Dialysis (BID) Pilot Study; Jennifer Gassman, Cleveland Clinic

P40 Multi-site Clinical Trials Protocol and Data Management Training: Overcoming Challenges in the Age of Technological Distraction; Suzanne Gillespie, Kaiser Permanente Northwest Center for Health Research

P41 ORDCRM: An R Package for Variations of the Likelihood-Based Continual Reassessment Method Design for Dose Finding Clinical Trials with Ordinal Toxicity Grading; Emily Van Meter, University of Kentucky

P42 A Multifaceted Approach to the Query Process; Trinh Hoac, Sunnybrook Research Institute

P43 Using Standardized Patients to Help Assess an Applicant’s Therapeutic Potential in a Psychotherapy Treatment Trial; Julie Weston, University of Toronto
Poster Presentations

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Poster Presentation Monday, May 16, 2011, 8:00 AM – 5:30 PM
Prime Time 10:00 AM – 10:30 AM and 3:00 PM – 3:30 PM

P44 What is Baseline and Change? An Example from Studies of eGFR.; Heidi Christ-Schmidt, Statistics Collaborative, Inc.
P45 Challenges of Reporting and Coding Adverse Events in Clinical Trials; Hua Carroll, KAI Research, Inc.
P46 Systematic Review of the Methods and Effects of Source Data Verification in Clinical Research; Roxanne Ward, Children’s Hospital of Eastern Ontario Research Institute
P47 Improving Clinical Trial Data Collection: A Web-based system to Dynamically Generate Study Forms with Integrated Barcodes; Darrin Harris, Wake Forest University School of Medicine
P48 A Center Performance Assessment Tool in a Multicenter Clinical Trails Network; Elizabeth Thom, George Washington University
P49 Enrollment and Compliance in a National Physical Activity Study: An Interim Report from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study; Virginia Howard, School of Public Health, University of Alabama at Birmingham
P50 A Model for Capitation Payment in a Multicenter Clinical Trial Network; Trisha Boekhoudt, George Washington University
P51 Normative Data and Implications for Randomised Controlled Trials; Suzanne Breeman, University of Aberdeen
P52 The Unique System for ‘Unnotified Clinical Trials to the Authority’ in Japan; Toshinori Murayama, Translational Reseach Center, Kyoto University Hospital
P53 Methodology and Challenges in Executing in Executing a Pediatric Cardiovascular Multicenter Randomized Clinical Trial for Off-label Drug Use.; Victor Zak, New England Research Institutes
P54 Analysis of Relatedness Terminology for Adverse Effects in a Phase I Clinical Trial; Marla Husnik, Fred Hutchinson Cancer Research Center

Poster Presentation Tuesday, May 17, 2011, 8:00 AM – 5:00 PM
Prime Time 10:30 AM – 11:00 AM and 2:50 PM – 3:20 PM

P55 A Latent Class Model Analysis Using the Monte Carlo EM Algorithm to Assess Accuracy of Diagnostic Tests of Cervical Neoplasia in Women with Atypical Glandular Cells of Undetermined Significance; Le Kang, University at Buffalo
P56 Meta-Analysis of Cardiac Surgical Trials Concerning Intramyocardial Bone Marrow Stem Cell Transplantation; Aenne Glass, University of Rostock
P57 Determining the Optimal Biomarker Cutoff for Defining a Subpopulation of Cancer Patients Who May Benefit from Treatment; Don (Dongguang) Li, Pfizer Inc.
P58 Implementation of Cognitive Screening and Confidentiality Assurance with an On-line Survey for Measuring Population Preferences; Colleen Peters, Washington University School of Medicine
P59 An Efficient Web-Based Approach to Managing a Complex Cause of Death Review Process; Jennifer Rosenbaum, Westat
P60 An Integrated, Interactive Web-Based Study Certification System; Ellen Peskin, University of Pennsylvania
P61 Creating and Supporting a Productive Environment for Ancillary Study Development in a Multicenter Trial; Brenda Brewer, Westat
P62 Automated Drug Ordering in a Cooperative Group Setting; William Elgie, GOG Statistical & Data Center
Poster Presentations

Order of Poster Presentations is subject to change – Please consult final program

Poster Presentation Tuesday, May 17, 2011, 8:00 AM – 5:00 PM
Prime Time 10:30 AM – 11:00 AM and 2:50 PM – 3:20 PM

P63 Retention of Clinical Trial Participants in a Study of Non-Gonococcal Urethritis (NGU), a Sexually Transmitted Infection; Jeannette Lee, University of Arkansas for Medical Sciences

P64 Gynecologic Oncology Group (GOG): Remote Paperless Study Chair Reviews; Angela Kuras, Gynecologic Oncology Group Statistical and Data Center

P65 Power Analysis of Nominal Agreement Among Multiple Raters; Zhibao Mi, VA Cooperative Study Program

P66 Single-visit Scale and Polish for Gingival health: The Results of a Primary Care RCT; Clare Jones, The University of Manchester

P67 Conditional Power Using an Information Based Approach to Determine Futility in Equivalence Trials; Uma Kher, Merck & Co.

P68 Challenges in the Design and Conduct of Controlled Clinical Effectiveness Trials in Schizophrenia; Robert Rosenheck, Veterans Affairs

P69 Strategies to Maximize Enrollment for Trials Requiring In-hospital Postpartum/Postnatal Recruitment; Katherine Trigiani, Sunnybrook Research Institute

P70 Exploring the Potential for Inconclusive Results from a Non-inferiority Trial; Allison Edwards, Jaeb Center for Health Research

P71 Transferring Randomized Participants - The Accord Model; Sharon Wilmoth, Wake Forest University Health Sciences

P72 Data and Safety Monitoring Policy for NIAID Clinical Trials; Dennis Dixon

P73 A Unique Web-Based Tool for Performing and Tracking Data Quality Assurance Tasks in a Multi-Center Study; Kathy Clingan, Westat

P74 Creating a Better, Shorter DMC Report: A Stack of Needles, Not a Needle in a Haystack; Shannon Grant, Axio Research

P75 Regional Collaborators’ Meetings for an International Study; Sonya Mergler, Sunnybrook Research Institute

P76 Design and Implementation of a New Query Management System; Cathy Yang, Sunnybrook Research Institute

P77 Double Data Entry Quality Control in URECA (Urban Environment and Childhood Asthma), a Multisite Longitudinal Study; Stephanie Hicks, Rho

P78 The Process of Developing an Online Randomization System; David Lau, Sunnybrook Research Institute

P79 Imputation of Incident Events in Longitudinal Studies; George Howard, University of Alabama at Birmingham

P80 A Case for Using Absolute Treatment Differences When Designing a Clinical Trial with a Dichotomous Outcome; Tony Panzarella, Princess Margaret Hospital

P81 Theoretical Error Rates of Qualitative UDS Tests for Stimulants; Neal Oden, The EMMES Corporation

P82 Effective Graphical Data Displays to Facilitate Expedited DSMB Review of Clinical Trial Data; Karen Boyle, Rho, Inc.

P83 Clustering in Surgical Trials: Database of Intra-Cluster Correlations; Jonathan Cook, University of Aberdeen

P84 Adjudication of Visual Field Endpoints in the Ocular Hypertension Treatment Study (OHTS); Mae Gordon, Washington University School of Medicine

P85 Control Groups in Caregiver Intervention Research: Issues and Dilemmas; Sara Czaja, University of Miami Miller School of Medicine

P86 Central Statistical Monitoring in Clinical Trials; Amy Kirkwood, University College London
Order of Poster Presentations is subject to change – Please consult final program

Poster Presentation Tuesday, May 17, 2011, 8:00 AM – 5:00 PM
Prime Time 10:30 AM – 11:00 AM and 2:50 PM – 3:20 PM

P87 Some Strategies for Report Generation by Biostatisticians in Clinical Trials; Jon Yankey, Clinical Trials Statistical and Data Management Center
P89 How Do We “Adapt” the Analysis Plan with the Protocol is Modified?; Yuko Palesch, Medical University of South Carolina
P90 Optimizing Trial Monitoring on the AZURE Trial; Geraldine Matthews, University of Leeds
P91 Applying Futility Analysis to Several Real Clinical Trials; IfteKharKhan, University College London
P92 Resolving Discrepant Slope Estimates from Simple Least Squares Versus Repeated Measures Regression; Brett Kaminski, Jaeb Center for Health Research
P93 Simulation Study of an Indication-Finding Trial Approach to Phase II Development; Heemun Kwok, Harbor-UCLA Medical Center
P94 Website Designed to Facilitate Data and Safety Monitoring Board Reviews; Brandy Lind, Rho
P95 Nonparametric Techniques for Method Comparison as Applied to Visual Acuity Scores Obtained with Automated Refraction versus Manual Refraction; Haijing Qin, Jaeb Center for Health Research
P96 Using Open Source Electronic Data Capture for Large Randomised Controlled Trials; Michael Shi, Sunnybrook Research Institute
P97 Developing a Final Analysis Timeline for a Large Multicentre Randomized Controlled Trial; Johanna Sanchez, Sunnybrook Research Institute
P98 Novel Therapies in Resistant FSGS (FONT II) Phase II Clinical Trial: Study Design and Update; Milena Radeva, Cleveland Clinic
P99 Adding Cohort Follow up to the End of a Randomized Trial; Jennifer Gassman, Cleveland Clinic
P100 Implementation of Cardiovascular Cell Therapy Clinical Trials; Points to Consider; Erica Anderson, The EMMES Corporation
P101 LA Red: The Formation of an Emerging Infectious Diseases Clinical Research Network in Mexico; Guillermo Ruiz-Palacios, Salvador Zubirán National Institute of Medical Sciences and Nutrition
P102 Action to Control Cardiovascular Risk in Diabetes (ACCORD) Home Blood Pressure Study Results; Annie Green Howard, Wake Forest University School of Medicine
P103 Development and Implementation of the Hierarchical Bayesian Design in Clinical Trials with Multiple Disease Types; Rui Qin, Mayo Clinic
P104 A Toxicity-adaptive Isotonic Design for Combination Therapy in Oncology; Rui Qin, Mayo Clinic
P105 Clinically Significant Effect Sizes for Survival and Response Endpoints Using the 1/2 Standard Deviation Rule; Amylou Dueck, Mayo Clinic
P106 Using the Heckman Model to Impute Indirect Financial Burden for the Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Trial; Lynn Huynh, Johns Hopkins Bloomberg School of Public Health
P107 Predictors of Blood Pressure Control at 6 and 12 Months in the Secondary Prevention of Small Subcortical Strokes (SPS3) Study; Lindsey Hornung, University of Alabama at Birmingham
Abstracts

Abstracts appearing in this SCT final program book are printed as submitted by the author(s) of that abstract. Unless instructed by the author, the content of the abstract was not edited or reformatted.

A01
DUPLICATE IDENTIFICATION USING NON-SENSITIVE INFORMATION
Zhibao Mi, Xiaoli Lu, Steve Bingham, Joseph Collins
VA Cooperative Studies Program, Perry Point, MD, USA

Duplicate cases in a clinical trial or survey database could jeopardize the data quality and integrity and induce biased analysis results, either inflating or masking treatment signals. These complications often happen in clinical trials, meta-analyses, and registry and observational studies. Traditional methods to identify possible duplicates involve sensitive personal information, such as name, social security number (SSN), date of birth, address, telephone number, etc.; however, access to this sensitive information is limited, and sometimes it is restricted. As a measure of data quality control, we propose a method to identify duplicated individuals using non-sensitve information, such as age, gender, race, medical history, vital signs, and laboratory measurements. A probabilistic approach was used by calculating weights for data elements used to identify duplicates based on two probabilities, i.e. probability of agreement for an element among matched pairs and probability of agreement purely by chance among non-matches. For elements with categorical values, agreement was defined as matching pairs sharing the same value, and for elements with interval values, agreement was defined as matching values within one percent of measurement precision range. Probabilities used to compute matching element weights were estimated using an expectation-maximization (EM) algorithm. The method was then tested on survey and clinical trial data from hypertension studies. The results showed that the potential duplicates identified using the highest score calculated from probabilistic weights included those found by the deterministic or exact match approach, and the probabilistic approach had higher sensitivity in duplicate case identification.

A02
PARTICIPANT DATA ENTRY FOR A WEB BASED DATA MANAGEMENT SYSTEM
Leah P. Griffin, Letitia H. Perdue, Mark D. King, Karen Erickson, Erica Ferguson, Judy L. Bahnson, Wei Lang, Mark A. Espeland
Wake Forest University Health Sciences, Winston-Salem, NC, USA

Wake Forest University School of Medicine serves as the Clinical Coordinating Center for the Study of Novel Approaches to Prevention (SNAP) Study. SNAP is a randomized clinical trial comparing interventions targeting large or small behavioral changes plus self-regulation to a control group using self-regulation alone. The primary outcome is weight change over three years. The trial will enroll 600 young adults between the ages of 18 and 35 years. The web based data management system (DMS) was designed to take advantage of the study design where primary recruitment is done on college campuses and internet access is an inclusion criterion. Participants complete a self-administered screening questionnaire and study forms online. The DMS was designed to include user friendly features for participants. Upon login, web-site navigation is minimized and participants arrive directly at the self-administered forms where access to forms is based on their visit window. The look, feel, and names of the self-administered forms are simple and straightforward. Forms covering similar topics are grouped into sections and the participants are provided with estimated times for form completion and the status of form completion. While the participants complete the self-administered study forms online, clinic staff members have the ability to review and edit these forms and complete data entry if needed. Designing a DMS with a primary focus on participant data entry has multiple advantages in this target population. Paperless data entry decreases the participant and staff burden. Participants can complete forms at their convenience. Clinic visit times are reduced. This presentation will elaborate on the design of a system built for participant data entry, describe additional features created for participant use such as the ability for participants to schedule their follow-up visits, and discuss the advantages and limitations of such a system.
Long term follow-up of clinical trial participants who have completed study intervention does not necessarily require in-person clinic visits. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) ended study intervention in 2008, and over the next 2 years, all 384 active study sites throughout North America discontinued follow-up responsibility for their participants. Long term follow-up of 15,656 participants consisted of an annual questionnaire administered from a central Coordinating Center.

Following a start-up period during which all the questionnaires were collected by mail, SELECT developed a secure website, MySELECTData, to accommodate those participants who prefer to complete their questionnaires on-line. The SELECT participant population consists of men at or near retirement age, and on-line entry is more convenient for those who travel extensively, divide their time between two residences or are technically savvy. After an initial start-up period, on-line entry is also less resource-intensive for the Coordinating Center. A major challenge when conducting follow-up by mail is maintaining current contact information. The questionnaires are mailed once a year but the secure website provides an opportunity for the participants to update their contact information as often as needed. Ability to maintain current contact information reduces the costs of remailing documents and staff time to update contact information.

Though SELECT has a long history of accepting study data through a secure website, creating a website for participants as opposed to trained study site personnel posed unique challenges. Developers adapted existing technology to create the MySELECTData website for this older population of participants (median age 69.8), taking into account special considerations for authentication, password management, ease of navigation, and clarity of edit checks. Eight participants from the Participant Advisory Board tested and provided feedback on the website. The secure website was promoted to all participants in the participant newsletter.

The Study of Novel Approaches to Prevention (SNAP) is a randomized clinical trial of 600 adults, aged 18-35 years, comparing weight gain prevention between small and large behavior change interventions and a control condition. Participants are directed to the SNAP website and are provided information about the study and the option to begin eligibility screening by entering personal information. Participants provide their contact information and answer several specific medical history questions on both an online and telephone screening prior to signing the informed consent document.

SNAP researchers created restrictions to ensure that protected health information (PHI) are not retained indefinitely for ineligible participants. This protects participants, while also allowing researchers to track study interest and reasons for ineligibility.

To ensure that the study does not become a registry, the online screener does not save to the study database when participants do not meet study age criteria. The database tracks the number of screeners submitted and not saved because of the ineligible age criteria. SNAP staff do not have access to this participant contact information.

While recruitment is ongoing, contact information on all age-eligible participants, regardless of eligibility, is retained to prevent re-screening. After recruitment has ended, all contact information for ineligible participants will be deleted. Responses to the specific questions are not retained in the database. In order to retain informa-
tion on reasons for ineligibility without identifying information, data are classified into broad groupings so as to remove the link between the participant and specific medical history and other sensitive materials.

It is critical to balance the ease and advantages of using online screeners with protection of the PHI that is collected via the screener. As studies move toward more internet screening methods, novel approaches are necessary to gather research data while maintaining the protection of participants.

**A05**  
**CHALLENGES OF CREATING AND MANAGING STANDARDS (COMMON DATA ELEMENTS) FOR USE IN CLINICAL TRIALS**

Patti Shugarts, Yun Lu, Stacie Trollinger, Kristy Miller, Selma C. Kunitz  
KAI Research Inc., an Altarum Company, Rockville, Maryland

To streamline the implementation of clinical studies, reduce start-up time and accelerate data aggregation across studies, the National Institutes of Health (NIH) together with KAI Research, Inc. (KAI), embarked on common data element (CDE) projects. KAI has developed a systematic approach to the development and implementation of data standards. These standards span the entire study lifecycle, facilitating study start up, data collection and management, and data archiving and sharing. With more and more CDEs developed, establishing standard approaches to manage CDEs becomes critical.

This abstract will provide information on the challenges with creating, implementing and managing standards. The challenges as well as our best practices in overcoming these challenges are:

- Keeping up with current standards (CDISC, caBIG, etc.) o Harmonization efforts ongoing o Regular communications with these groups key
- Reviewing the Literature o Including references for the CDEs adds credibility o Publications may lack detailed data management information
- Limiting the universe o Identification of core CDEs (those most essential for data collection) o Build from existing forms to gain buy in from the clinical research community
- Creating a team of experts o Identifying who should be part of the team o Advantages and disadvantages to top down vs. bottom up development
- Establishing standard procedures for standard development o Development of standard procedures in parallel to standards o Internal standard review committee for quality and consistency
- Tools to enhance use o Dictionary, template forms, suggested edits, data management plan (DMP), etc. o Website design/ layout - making it user friendly.

The process for creating, implementing and managing standards has been met with many challenges but the benefits outweigh the frustrations. CDEs and standards have demonstrated enhanced data quality, decreases the time and resources needed to develop a study database, and helps customize the DMP.

**A06**  
**DEVELOPING STATISTICAL STANDARDS IN AN ACADEMIC DATA COORDINATING CENTER**

Amy E. Donaldson, Angie S. Webster, Richard Holubkov, J. Michael Dean  
University of Utah, Salt Lake City, UT, USA

The genesis of an academic data coordinating center (DCC) can be quite different than that of for-profit or other non-profit DCCs. Often an academic DCC is established based on an identified need for a particular clinical area or in response to a call for proposals by a funding agency. Initially there may be limited resources and infrastructure, and academic research personnel may not be familiar with the rigorous requirements for the management and support of multi-center clinical trials. One of the critical components to DCC success is establishing guidelines to ensure quality and consistency in the statistical support provided, particularly in dataset programming and statistical analyses. The DCC at the University of Utah was established in 2002 in support of a single multi-institutional research network and two studies. We now support four multi-institutional research networks and over 30 active projects. This growth has prompted us to develop and implement statistical standards that promote the quality, timeliness, and reproducibility of all analysis datasets and results. Key aspects of these
standards include (1) database testing and review of test datasets prior to enrollment start; (2) the use of a
template for analysis dataset specifications; (3) an assessment of risk associated with coding errors for each
aspect of the project; (4) dual (independent) programming and/or peer review of analysis dataset code; (5) dual
verification of analyses and results; and (6) ongoing documentation of analysis decisions. In addition, these
standards emphasize close interaction and collaboration with data and project managers in all aspects of the
study. This presentation will provide practical guidance on developing and implementing these types of standards
in an academic DCC.

A07
ELECTRONIC HEALTH RECORD AND CLINICAL TRIALS:
ADVANTAGES AND DATA QUALITY ISSUES
Reza Rostami
Duke Clinical Research Institute, Durham, NC, USA

The abundance of data collection, aggregation, exchange and replication in the electronic world magnifies con-
cerns over data quality. These are particularly important in the medical field, where data problems represent
the dark side of the tremendous potential offered by the adoption of health IT systems (Connecting for Health,
2006). In focusing on the complications of Electronic Health Record (EHR) software application development,
data quality concerns are often moved to the bottom of the priority list. The Institute of Medicine reported in
2000 that in the United States, approximately 98,000 people die annually because of medical malpractice dur-
ing hospitalization (IOM, 2006). Poor data quality is believed to be one of the main factors contributing to mal-
practice, the increasing cost of healthcare and the loss of human lives. Without high quality data it is difficult to
monitor the quality of care, have reliable pay- for-performance programs, or assess the effectiveness of quality
improvement initiatives or evidence-based medicine. Poor data quality decreases reliability and trust, creates
liability risks, increases cost and inefficiencies, and most importantly, impacts the quality of patient care. In the
near future, through full implementation of EHR within health care facilities in the United States, the only patient
source data for use in clinical trials will be in electronic health records. Assuming the technical issues such as
standardization and interoperability have been resolved by then, the gap between the data quality needed for
clinical trial research and what is needed for routine clinical work must be explored, managed, and closed. This
presentation explores issues of data quality when data from EHR systems are used as source data for clinical
trial research.

A08
METADATA AS THE KEY TO SEMANTIC INTEROPERABILITY IN CLINICAL DATA SYSTEMS
Brian Campbell, David Shide, Sherita Alai
EMMES Corporation, Rockville, MD, USA

The future of biomedical research demands increased interoperability between disparate data systems and more
access to research data. Since 2002, EMMES has worked to support the development and implementation of
common data elements (CDEs) on several of its NIH-sponsored clinical trial contracts, and has participated in
numerous working groups to help define the rules for metadata exchange. CDEs are metadata descriptors of data
represented on case report forms (CRFs), and are governed by ISO 11179, an internal standard for the creation,
storage, and exchange of metadata.

The process begins with the development of CRFs by the sponsoring authority. These CRFs are then submitted to
the EMMES CDE team for CDE-compliance review. Questions and permissible value sets used on the CRFs are
compared to the appropriate approved standards (CDISC, NCI CRF Harmonization Group, CTCAEv4, AJCC 7th Ed.,
RECIST, etc.). If outstanding issues are identified, EMMES works with the sponsor to bring the CRFs into CDE com-
pliance. During this process a metadata representation of each CRF, using existing and/or new CDEs, is created in
NCI’s metadata repository. Once the CRFs are approved as compliant, the eCRFs are used by: OPEN, NCI’s online
patient-registration data system, for data exchange with the sponsor; RAVE, NCI s electronic clinical data-capture
system, for development and implementation by the sponsor; and, caBIG, the NIH’s biomedical informatics grid, for
storage and exchange of clinical and preclinical data for use by the larger research community.
Without a common semantic language of well-constructed metadata, the ultimate potential of these interoperable data systems will be reduced. This presentation will provide details on CDE creation and registration and describe the ways in which CDEs support, enhance, and streamline interoperability and data access.

**A09**
**EXPLORING A DATASET FOR PROACTIVE IDENTIFICATION AND OVERLAP CHECKING OF PLANNED POLICY RELEVANT CLINICAL TRIALS**

**Andrew Cook, Eleanor Woodford-Guegan**

*NETSCC, University of Southampton, England*

Publicly funded research funders have a duty to make best use of their limited resources. Part of the way they can do this is by minimising overlaps in funded research or where overlaps occur maximising the opportunity for merging data collected, for example by facilitating meta-analysis. There is however no robust way for funders to determine what other organisations are planning. While there are registries for trials which have been funded, by the time a funder becomes aware of a study via a trial registry a funder may have already committed itself to a similar, but not meta-analysable study. This was the experience of the UK’s NIHR HTA Programme, the French Institut National du Cancer and New Zealand’s PHARMAC. In 2007 all three organisations commissioned projects on trastuzumab in breast cancer, which were sufficiently different to be difficult to subsequently meta-analyse. This presentation discusses the development of a dataset to enable rapid information exchange on planned trials, to prevent this situation happening in future. Development involved funders and triallists across three continents. We discuss the issues of dataset development, and present the final agreed dataset. We also outline the future process which will result in a registry launching in 2012.

**A10**
**THE EFFECT OF SHORT MESSAGING SERVICE (SMS) USE FOR SUBJECT COMPLIANCE IN CLINICAL TRIALS**

**Keiko Sing, John Kyle Apostolides, Devin J. Hunt, Nicole C. Close**

*EmpiriStat, Inc., Mt Airy, MD, USA*

According to one study nearly 1.5 trillion SMS messages were sent in the Asia-Pacific region in 2007, accounting for nearly 78.9% of SMS traffic worldwide (including North America and Western Europe). There is growing interest in the use of SMS to improve subject compliance and retention in clinical trials, making it a viable option in comparison to traditional compliance methods (top down methods such as fridge magnets or enewsletters). The low cost, instantaneousness, and ease of use makes SMS ideal for reminders, subject education, data collection, and encouraging continued study compliance. With data encryption of 256 bits, patient consent obtained before communication, and an “opt-out” service, all HIPPA and EU regulations are followed.

Randomized clinical trials from 1 January 2000 to 31 December 2010 that met certain criteria from the New England Journal of Medicine (NEJM) and the Journal of the American Medical Association (JAMA) were evaluated for the effect of SMS usage on subject compliance. Trends of SMS use were first tracked over the decade, in the US and globally. These trends were then compared to use reported in the trials. Trials using SMS were compared to other similar trials without use of SMS. Function of SMS included patient reminders and data collection. Preliminary results show that subjects using SMS in a clinical trial has improved compliance over those subjects not engaged in SMS methods. Further evaluation of advantages and disadvantages of SMS in clinical trials will be discussed in accordance with current SMS technology and 3G capabilities. Based on the preliminary meta-analysis, SMS text usage appears to be a feasible, cost effective technology for improving subject compliance in clinical trials.
A site performance monitoring module has been integrated into a web-based clinical trial management system (CTMS) for a large multicenter stroke trial, in order to provide real-time study progress and site performance information to study coordination centers as well as individual site study teams. Antihypertensive Treatment in Acute Cerebral Hemorrhage-II (ATACH-II) is a phase III multicenter trial in patients with intracerebral hemorrhage (ClinicalTrials.gov Identifier: NCT01176565). The trial is planned to recruit 1,280 subjects from 100 domestic and international sites in a 5-year period. A central statistical and data management center coordinates all data management activities and international Clinical Research Organizations (CROs) are contracted to provide trial management support for clinical sites in their domestic region. In addition to the common issues associated with large multicenter trials conducted in emergency settings, such as the high risk of trial operation errors related to the high paced work environment in emergency departments, the diversified data quality and protocol compliance levels caused by the varied research experiences and frequent personnel changes in site study teams, the involvement of large numbers of international sites and the use of foreign CROs creates special challenges that call for robust information tools for site performance monitoring. The web-based CTMS developed for the ATACH II trial is powered by an integrated site performance evaluation metric that provides summarized and searchable information on subject recruitment, subject study progress, Case Report Form (CRF) data collection timeliness and completeness, Data Clarification Request (DCR) processing, protocol violations, Serious Adverse Event reporting, regulatory document collection and tracking, and findings from site data monitoring visits conducted by monitors supervised by the regional CROs as well as the central coordination center. Experiences and lessons learned from conducting an international trial will be shared in this presentation. This research is supported by NINDS grant R01 NS061861.

The multidisciplinary collaboration required for case report form development may lead to significant delays and miscommunications. Investigators are often pressured to begin the study without fully realizing the analyses required to properly create case report forms and the statistical implications of the data which is being captured. Pressures from sponsors may lead to development prior to funding which could result in wasted effort if funding falls through. After funding, it may not be clear which person is currently responsible for moving the development process forward or that the team is awaiting a decision from either the principal investigator or biostatistician. Over the course of a year, we have refined the case report form development process into three phases with clear steps that demarcate the responsibilities of the form developer, the principal investigator’s team, the statistician, project managers, and quality assurance. An initial phase collects requirements, creates draft mockups, and receives preliminary approval from the collaborators prior to funding. After funding, form development proceeds in a test environment and data exports are validated. The final phase encompasses migration of forms to the production environment and final quality assurance. Our process accommodates embedding code such as javascript within electronic case report forms which is not a standard process for the trial management software vendor. We find that visually describing this process and tracking status of our studies has reduced confusion and enhanced transparency amongst all research colleagues.
EXPERIENCES OF THE NINDS CLINICAL RESEARCH COLLABORATION WITH THE USE OF A VIRTUAL COORDINATOR
Carolyn Burke, Anne Lindblad
The EMMES Corporation, Rockville, MD, USA

The Chronic Migraine Treatment Trial was a randomized double blind placebo controlled trial to test the efficacy of combination prophylactic therapy in chronic migraine patients. This study offered a virtual clinical research coordinator to sites which, due to a lack of staffing resources, may not otherwise have been able to participate in research. The CRC virtual coordinator was to collaborate with investigators and subjects from each site requesting such services by performing the traditional role of a clinical coordinator remotely from the NINDS CRC Operations Center. Specifically the virtual coordinator was available to assist the physician with CRF completion, data entry, informed consent process, subject follow-up and protocol adherence. Four of the 70 activated centers elected to utilize this option. One of these centers enrolled 14 subjects and randomized 6 subjects; one screened 3; one screened 1, and one site failed to screen a single subject. The site that randomized 6 subjects was in the top 20 percent of enrolling sites.

Challenges to implementing this approach included: "Completion and storage of source documentation that ensured site staff and the virtual coordinator have access to current study subject information while maintaining confidentiality " Coordinating schedules for study visits and virtual coordinator availability between the subject, the clinic site, and the CRC coordinator “ Ensuring that all consent procedures and study activities were completed for each subject “ Ensuring that site staff appropriately determined eligibility prior to forwarding subject contact information to the virtual coordinator “ Minimizing the potential for discrepancies between the coordinator and physician

The virtual coordinator model allowed physicians to actively and productively participate in research. The challenges with the virtual aspect are ones that are unlikely to be conducive to wide spread adoption of this approach.

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RETENTION STRATEGIES, METHODOLOGY AND CONSIDERATIONS: AN EXAMPLE FROM A 3.5 YEAR PROSPECTIVE, CLOSED, COMBINED COMMUNITY/WORKPLACE CLINICAL EPIDEMIOLOGICAL STUDY IN KENYA
Nicole C. Close, Doug Shaffer, John Mokaya, Elmelda Obiero, Peter Yegon, Argwings Miruka, Fredrick Sawe, Samuel Sinei, Paul Scott, Merlin Robb
EmpiriStat, Inc., Mt Airy, MD, USA

Little data exists on participant retention among adults in long term HIV clinical research studies conducted in rural communities in Africa. An understanding of factors affecting retention in this setting are critical in planning and conducting research in which high retention rates are clinically necessary. Baseline questionnaires on medical, behavioral and social history (including HIV risks) and HIV testing was conducted in this 3.5 year clinical epidemiological study as well as visits every 6 months. Retention was defined as compliance to study visit schedules without setting a limit or range as to when the participant completed the questionnaire, but with an unwritten goal of 80% retention at the final study visit. Various retention strategies were used (focus group discussions, active volunteer tracing, free medical care for participants and dependents, volunteer compensation, study staff empowerment) and the impact of these will be discussed in relation to observed retention rates. Retention varied from 10.6% to 81.4% for one set of analyses (see Table). All baseline demographics examined with respect to retention definitions, and retention was assessed for those who became HIV+ and those who did not. Retention will be evaluated in relation to the following methodology considerations: 1. Magic number syndrome (good vs. bad); 2. No simple definition of compliance/response rates; 3. Non-participation bias; 4. Extreme efforts to raise compliance (not necessarily good!); 5. Statistically look at data (censor time, MCAR, MAR, NIM); 6. Report several response rates with careful explanation; and 7. Generalizability of findings

A multi-faceted approach for retention should be implemented to control for different aspects of loss-to-follow-up and collection of information prospectively in regards to retention. There are a number of different ways to
analyze retention which yields different information and most importantly there is interplay among cultural, demo-
graphic, health status, personal and family factors that affect retention.

A15
INTERVENTION TO IMPROVE RECRUITMENT TO RANDOMIZED CONTROLLED TRIALS
Jenny Donovan, Joy Adamson, Nicola Mills, Julia Wade,
Sangeetha Paramasivan, Athene Lane, Jane Blazeby
School of Social and Community Medicine, University of Bristol, UK

Aims and Introduction: Pragmatic multi-centre RCTs are the design of choice for evaluating the effectiveness of
health care interventions but there are concerns about the number of RCTs that experience recruitment diffic-
tulties and so are terminated before completion, require expensive extensions, or have limited statistical power and
selection biases. Reviews of strategies to improve recruitment have found studies of poor quality with impact
limited to specific RCTs.

Methods: A synthesis of studies of recruitment to ongoing RCTs was undertaken to (a) understand the sources
of recruitment difficulties and (b) to develop an intervention to improve recruitment to RCTs in a wide range of
contexts.

Results: The synthesis produced a detailed understanding of how recruitment was undertaken in six very dif-
ferent RCTs, showing that poor recruitment was indicative of problems with the design and/or conduct of the
RCTs. Factors such as over-elaborate recruitment pathways, poor understanding of aspects of the RCT design,
poor communication between RCT designers and clinical staff, perceived conflicts between clinical and research
roles among recruiters , a lack of equipoise expressed by some clinicians, and strong treatment preferences
expressed by potential participants all hindered recruitment. An intervention was developed based on these find-
ings and then applied to another RCT with poor recruitment. Phase one involved exploring the evidence base,
patient eligibility, levels of equipoise and the practicality of the RCT protocol. Phase two involved the implementa-
tion of a dedicated plan to resolve problematic areas of design/conduct and provide training for generic issues
of communication and treatment preferences.

Conclusion: An intervention in two parts has promise for application to RCTs to improve levels of trial participation.

A16
DYNAMIC EVOLUTION OF THE STUDY COORDINATOR ROLE:
THE 27 YEAR EXPERIENCE IN DCCT/EDIC
Mary E. Larkin, Gayle M. Lorenzi, Meg Bayless, Patricia A. Cleary,
Annette Barnie, Ellen Golden, the DCCT/EDIC research group
Boston, MA, USA; San Diego CA, USA; Iowa City IA, USA;
Rockville MD, USA; Toronto, Ontario, Canada; Bethesda, MD, USA

Abstract: Diabetes Control and Complications Trial (DCCT) was a multicenter interventional study that estab-
lished the relationship between glycemic control and complications in type 1 diabetes. This cohort continues to
be studied in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. DCCT/EDIC requires
teamwork among clinical sites, reading centers and coordinating center. Due in great measure to the effort and
commitment of DCCT/EDIC study coordinators, more than 95% of 1359 surviving patients continue to return for
annual EDIC evaluations. The coordinator role has evolved from implementation of the study protocol to involve-
ment in leadership and decision-making.

The medical model dictated early organization of the DCCT, with physicians responsible for protocol design and
study management decisions. Coordinators were responsible for protocol implementation, data-collection, dia-
betes management, and patient/family education and support. Formation of a coordinators committee provided
a forum for dealing with patient education and advocacy, diabetes management, and participant / staff relation-
ships and retention and coordinators acquired more active role in decision making locally and study-wide.

EDIC expanded the role of coordinators, as they became voting members of the Study Group, chairs of study-wide
committees, participated in research decisions, co- investigators of ancillary studies, participated in the publica-
tion and presentation of study results and maintained responsibility for participant retention. The coordinator
committee facilitates mentoring for new coordinators, fosters development of clinical expertise in diabetes treatment, develops new research initiatives, and is responsible for the initiation of ancillary study procedures.

DCCT/EDIC coordinators have achieved professional accomplishments that extend beyond the traditional coordinator role. Increased autonomy, accountability and responsibility have been supported by the NIDDK and have contributed to the success of this research enterprise.

A17
RECRUITMENT METHODS EMPLOYED IN THE NATIONAL LUNG SCREENING TRIAL (NLST)
Pamela M. Marcus¹, Suzanne Lenz², Donna Sammons³, William Black², Kavita Garg³
¹ National Cancer Institute, Bethesda, MD, USA; ² Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; ³ University of Colorado Denver, Aurora, CO, USA

Background: The NLST is an RCT designed to determine whether screening with low dose helical computed tomography versus single posteroanterior chest radiograph can reduce lung cancer mortality. Thirty-three US medical centers recruited 53,454 participants using varied methods. Purpose: We describe methods used to recruit participants and the extent to which each method was used. We provide costs per enrollee for some screening centers and some methods. Methods: After recruitment was completed, screening center coordinators were asked to complete a three-part questionnaire. The first part asked coordinators to rate, using plusses and minuses, the extent to which specific methods were used. The second part asked coordinators to provide, for each specific method, numbers enrolled and total cost of the effort. Cost per enrollee was calculated. The third part asked coordinators to report lessons learned from the recruitment effort. Results: Twenty-two screening centers returned questionnaires. Use of recruitment method varied by screening center, but overall, direct mail and mass media were used more extensively than community outreach. Among centers reporting number enrolled by method, more participants were enrolled with direct mail (approximately 19,000) than with mass media (approximately 4,200). Mean costs per participant enrolled were as follows: direct mail - $117 (range: $6-$325); community outreach - $21 (range: $0-$103); mass media - $335 (range: $0-$1,953). Coordinators reported that it was important to know your target population, that is, to know where to find persons who are likely to be eligible and interested, and how best to approach them. Limitations: Data were unavailable for 11 NLST screening centers. Success of recruitment method was based in part on subjective measures. Some data were collected retrospectively. Conclusions: In terms of yield and cost, direct mail appeared to be the most successful recruitment tool. Future studies of recruitment success should collect recruitment data prospectively.

A18
MID-RECRUITMENT TRAIL REDESIGN TO INCORPORATE GENETIC SUB-TYPES
Catherine Olivier, Sarah Brown
Clinical Trials Research Unit, University of Leeds, Leeds, UK

PICCOLO is a multicentre, phase III, advanced colorectal cancer trial, comparing Irinotecan alone (Ir) with Irinotecan plus Ciclosporin (IrCs) for patients with KRAS mutated or undefined tumours, and with Irinotecan plus panitumumab (IrPan) for patients with KRAS wildtype tumours. The trial is designed as two parallel phase III trials, accounting for patients KRAS status. PICCOLO was originally designed in 2006 with equal randomisation between all three arms, regardless of KRAS status. However, in light of emerging data showing no benefit of treatment with monoclonal antibody therapy for patients with mutated or undefined KRAS status, the trial was redesigned. Recruitment became a two-stage procedure: registration to identify KRAS status, then randomisation based on this. The redesign presented a number of challenges. An urgent safety measure was implemented whilst the protocol was amended and gained the necessary approvals; both processes adversely affected recruitment. A number of sites did not wish to implement the new design as KRAS status was not revealed to treating clinicians or patients (in order to maintain recruitment to both comparisons and prevent early withdrawal from the control arm). The new processes of obtaining pathology blocks, performing KRAS testing, and obtaining results for randomisation required additional manpower and impacted on the time between subject identification and trial entry. Retrospective KRAS testing was necessary to ensure data from patients randomised prior to the redesign was used in the appropriate comparison at final analysis, requiring large scale chasing of tumour material. Trials requiring a mid-recruitment redesign may become more common as further genetic advances are made. Additional detail on the hurdles faced by PICCOLO, along with points for consideration, will be presented.
THE POTENTIAL FOR CENTRAL MONITORING TECHNIQUES TO REPLACE ON-SITE MONITORING IN CLINICAL TRIALS: A REVIEW OF MONITORING FINDINGS FROM AN INTERNATIONAL MULTI-CENTRE CLINICAL TRIAL

Julie Bakobaki, Mary Rauchenberger, Nicola Kaganson, Sheena McCormack, Sally Stenning, Sarah Meredith

Medical Research Council Clinical Trials Unit, London, England

Background: Over the last decade there has been a shift in the public sector towards on-site monitoring and source data verification to check protocol adherence and GCP, in response to new legislation rather than empirical evidence of effectiveness.

Design and Methods: retrospective analysis of findings documented in on-site monitoring reports from the Microbicides Development Programme 301 trial - a randomised placebo-controlled trial of a microbicide gel to prevent vaginally acquired HIV infection in 4 countries in sub-Saharan Africa. Each finding was extracted and assessed to determine whether it could have been detected in the trial database or through other central means.

Results: 268 monitoring findings were reviewed from 4 reports, assessing 104 participant files, covering 324 study visits. 75 (28%) of these findings were also flagged in the trial database. Central checks could have identified an additional 141 (52.6%), had they been specified and implemented (e.g., central receipt and review of back-translated documents, enrolment and testing logs, informed consent, and more complex database queries). 38 (14.2%) trivial findings identified from comments or errors made on the CRFs and 14 (5.2%) other findings could only be identified through an on-site review of the participant folder. None of these 52 findings posed a significant concern to participant safety or data integrity.

Conclusions: Whilst there are clear benefits to visiting trial sites (in particular staff motivation and training), and whilst not all categories of findings can be identified centrally, the majority of findings reviewed in this analysis could be identified using central strategies. These data suggest that with better central and targeted on-site monitoring it should be possible to prevent, identify and address most protocol and procedural compliance issues without performing intensive on-site data monitoring: meaning a more cost-effective model for ensuring adherence to the protocol and GCP in large clinical trials.

ACADEMIC TRIALS AND THE CHALLENGE OF SPONSOR RESPONSIBILITY

Andrea Grunow, Christine Georgias, Ursula Paulus

University of Cologne, Clinical Trials Center Cologne*, 50935 Cologne, Germany

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With the Amendment to the German drug law (AMG) in 2004 the performance of clinical trials changed by at least two main aspects: (1) the principles of good clinical practice (GCP) were implemented in national legislation and (2) for the first time the function of the Sponsor of a clinical trial and the Clinical trial (CT) itself have become legally binding definitions. By that, legal differences between industrial and academic CTs no longer exist. CTs sponsored or initiated by investigators (IIT) have to fulfill same requirements while the entire responsibility has to be carried out by the initiating investigator (CI) or his institution including implementation of a quality-management-system according to GCP. The Cologne sponsor model presents a functional approach with settings, structures, basic features, action- and reporting lines as well as funding for CTs in academic environment. The University of Cologne is declared as the sponsor according to law. Sponsor’s duties are delegated initially to a central operational unit of the sponsor - the Clinical Trials Center Cologne (CTCC) - which further delegates to the CI. CTCC was established to support the performance of clinical trials at University by offering comprehensive advisory and practical services covering all aspects of study planning and conduct. Furthermore a specialized division of its QM-department acts as an independent sponsor’s quality assurance unit (QAU). This QAU has established a QM-system consisting of different modules (1) to enable a reasoned decision to subsequent delegation, (2) for a risk-based surveillance of trial conduct (audits, monitoring-checks, reports) and (3) supporting and training of CI (SOP-templates, advice on QM issues, introductory IIT-manual). With this mixture of central management, control and support, our model represents a risk-based system that offers a sensible option fulfilling the requirements of legal regulations and Good Clinical Practice for the university environment.
A21

PEER REVIEW INTERVENTION FOR MONITORING AND EVALUATING SITES THAT IMPROVED RANDOMIZED CONTROLLED TRIAL CONDUCT AND PERFORMANCE

J. Athene Lane, Susan Bonnington, Liz Down, Teresa Lennon, Peter Holding, Amanda Jones, Elizabeth Salter, David Neal, Freddie Hamdy, Jenny Donovan

School of Social and Community Medicine, University of Bristol, Bristol, UK

Aims and Introduction: Good clinical practice guidelines (GCP) emphasize trial site monitoring, although the implementation is unspecified and evidence for benefit is sparse. We aimed to develop an on-site monitoring process utilising peer reviewers to improve staff training, site performance, data collection and GCP compliance.

Methods: The Peer Review Intervention for Monitoring and Evaluating sites (PRIME) team observed and gave feedback on trial recruitment and follow-up appointments, held staff meetings and examined documentation during annual two day site visits. The intervention was evaluated in the ProtecT trial, a UK randomised controlled trial of localised prostate cancer treatments (ISRCTN20141297). The ProtecT coordinator and senior nurses conducted three monitoring rounds at eight sites (2004-2007). The process evaluation utilised PRIME report findings, trial databases, resource use and a site nurse survey.

Results: Adverse findings decreased across all sites from 44 in round one to 19 in round 3. Most findings related to protocol adherence or site organisational issues including improvements in eligibility criteria application and data collection. The proportion of findings was distributed evenly across all sites. Findings suitable for analysis with trial databases showed improvements in return of consent forms and treatment CRFs. Staff found site monitoring acceptable and made changes following reviews. Total costs/annum ranged from 32 (one day reviews) to 56 days (2) of staff time and up to $7337 of direct costs (transport and accommodation).

Conclusion: The PRIME process utilised observation by peer reviewers to improve protocol adherence and train site staff which increased trial performance and consistency.

A22

HARMONIZED STANDARD OPERATING PROCEDURES FOR ACADEMIC TRIALS*

* Granted by the German Federal Ministry of Research and Education, Germany, BMBF 01EZ0931
Heike Moenkemann, Miriam Olderog, Ursula Paulus for the QM working group of the CTC-network
University of Cologne, Clinical Trials Center Cologne, 50935 Cologne, Germany, BMBF Grant 01K0706

Standard Operating Procedures (SOPs) are essential instruments of quality management (QM) in clinical trials. According to ICH-GCP (5.1.1) the sponsor is responsible for implementing quality assurance and quality control systems with written SOPs. Until 2000 SOPs were rarely used in German Investigator Initiated Trials (IITs). This began to change essentially with the foundation of Clinical Trial Centers (CTC) by the Federal Ministry of Education and Research (BMBF) in 1999 and the 12th amendment of the German Drug Law (AMG, 2004). These CTCs are central support units at university hospitals all over Germany and constitute a network. The goal of this network was the development of operational competence in clinical trials according to Good Clinical Practice considering the characteristics of IITs. A QM working group consisting of representatives of each CTC, supported by Technology, Methods, and Instructions for Networked Medical Research (TMF e.V.) and again by BMBF, developed a collection of harmonized SOPs. These cover central topics like project-, data- and quality-management, adverse events, statistics for clinical trials essential for the conduction of national and international trials. The harmonization of the SOPs improves the cooperation within the CTC-network considerably especially for multicenter trials. Since 2008 the CTC-network applied its expertise to develop SOP-templates dealing with all operational processes during clinical trials at study sites. All SOPs developed by the CTC-network are accessible on the TMF homepage for all interested parties free of charge. A wide circulation of these harmonizes SOPs is recorded. This SOP-project has become a major instrument for a sustainable advancement of IITs making the CTCs equal partners in clinical trials according to authorities and industry. Our report will deal with the challenge of implementing harmonized processes in a federal structure and SOPs-templates at study sites.
A23
SOLUTIONS FOR MONITORING MEDICAL RECORD ABSTRACTION QUALITY IN A MULTI-CENTER STUDY
Nancy Payte, Brenda Brewer, Kathy Clingan, Ellen Martinusen, Pete Ohan
Westat, Rockville, MD, USA

The National Lung Screening Trial (NLST) is a randomized controlled trial designed to determine whether screening with low-dose helical computed tomography reduces lung cancer mortality relative to screening with conventional chest x-ray in persons at elevated risk of lung cancer. Lung cancer diagnosis, a critical outcome of the study, still relies on data collected from medical records. The challenges of this large multi-center study included providing comprehensive training on the NLST medical record abstraction protocol and ensuring adherence to quality assurance methods that enhance the reliability and validity of data obtained from medical records.

To meet these challenges, a training program for medical record abstractors was developed and implemented. An operating procedures manual, with detailed specifications, provided the foundation for the abstractors. Initial centralized training was critical to ensuring abstractor comprehension of all study forms and data elements. An ongoing training component, either individual or group, provided the opportunity for review, discussion and clarification of abstracting guidelines. Quality assurance (QA) methods included review of the first ten charts completed by each abstractor and central re-abstraction of all primary lung cancer cases and a random sample of non-lung cancer cases. More than 3,000 charts were reviewed and any discrepancies found on comparison of the original abstracts and re-abstracts were adjudicated by the medical record abstraction coordinator. These QA approaches facilitated consistency and accuracy in the data collected and allowed for continuous feedback throughout the abstraction process.

In studies requiring medical record abstraction, it is vital to develop thorough standardized training and QA approaches. We will demonstrate how our program addressed the challenges and explore lessons learned in monitoring medical record abstraction utilizing this QA process.

A24
A WEB-BASED STUDY PRODUCT VERIFICATION UTILITY FOR BLINDED TREATMENT OF FOOD ALLERGY SUBJECTS
Daniel C. Rosenberg, Glenn Tucker, Ian Barrow
The EMMES Corporation, Rockville, MD, USA

Subjects in the NIH/NIAID funded Consortium of Food Allergy Research (CoFAR) receive blinded study product. To ensure that each subject receives the correct product, we designed a web-based utility for the Study Coordinators to verify that the pharmacy distributed product is appropriate for the subject ID. This is an important additional safety check as exposure to a food allergen can lead to anaphylaxis, a potentially life-threatening reaction. Therefore, correct dispensation is imperative.

For each protocol, the study product manufacturers and/or distributors provide a list of product IDs, whether the contents are active or placebo, and the clinical sites to which the product ships. Using this information and the enrollment system’s randomization scheme, we were able to design the utility databases to handle specific protocol needs. For example, one protocol requires complete kits and single vials provided to the subjects as needed. Another protocol assigns a multi-vial kit, but the vials are provided to the subjects one-at-a-time.

Study Pharmacists are not blinded and label the study product with the subject ID on dispensing days. Using this utility, Study Coordinators stay blinded while verifying that subjects receive the correct product. Prior to releasing product to the participant, Coordinators execute the web utility and a screen provides the user with a large colored graphic and message verifying success or failure. In the event of a failure, the message instructs the Coordinator to call the Statistical and Clinical Coordinating Center (SACCC) for further instructions. The utility emails the details of each verification success and failure to SACCC personnel.

For each protocol, the utility maintains two databases: 1) product assignments, and 2) each verification. These databases allow for data quality cross checks, automated reports, and the resolution of incorrect validations. Considerations for additional functionality include verifying valid changes in strength/dosage level.
Objective. Several randomized controlled trials comparing laparoscopic and open surgery for colorectal cancer have been published. This study sought to synthesize the oncologic outcomes associated with these trials, and to determine whether expert acceptance of this technology has paralleled the accumulation of survival evidence.

Methods. A comprehensive systematic review of the literature was conducted. Randomized controlled trials (RCTs) were retrieved and data abstracted. The primary outcome was survival. A meta-analysis of survival time-to-event data was conducted using described techniques. Hazard ratio estimates were generated from Kaplan-Meier curves. Reviews, guidelines, and textbook chapters were also included and used to grade expert opinion on a 7-point Likert scale. Pooled survival data were correlated in time with accumulating expert opinion scores.

Results. A total of 5,799 citations were screened. Of these, 42 publications pertaining to 25 individual RCTs were retained. As well, 413 reviews were included (28 guidelines, 30 textbook chapters, 19 systematic reviews, 336 narrative reviews). In total, 6,488 patients were randomized to laparoscopic (n=3,412) and open (n=3,076) colorectal surgery. Methodological quality was highly variable. Survival data was presented in 20 publications. The pooled hazard ratio for overall survival comparing laparoscopy to open surgery was 0.92 (95%CI 0.79, 1.06), p=0.25. The mean reported follow-up time ranged from 12-91 months. Expert opinion in the literature pertaining to the oncologic acceptability of laparoscopic surgery for colon cancer correlated most closely with the publication of large RCTs in 2002-2004. Laparoscopic rectal cancer surgery was widely perceived by experts as experimental. Conclusions. Laparoscopic surgery for colon cancer appears to be equivalent to open surgery in terms of oncologic outcomes. Expert opinion in the literature has been increasingly supportive of this finding since 2003. Laparoscopic surgery for rectal cancer remains controversial and is widely considered experimental, likely owing to the lack of large-scale RCTs.

A26
STATISTICAL ISSUES IN THE DESIGN OF RANDOMISED SURGICAL TRIALS: A PRACTICAL EXAMPLE OF THE POSSIBLE SOLUTIONS
Helen Marshall, Ivana Holloway, Julia Brown
Leeds, West Yorkshire, UK

Surgical randomised trials often have unique design and implementation issues: this abstract presents three key statistical issues accounted and the solutions adopted during the design of an international, randomised, surgical trial (ROLARR), comparing laparoscopic versus robotic-assisted surgery for rectal cancer patients, performed at the Clinical Trials Research Unit.

One significant issue for surgical trials is to ensure surgeons recruiting to the trial are over their initial ‘learning curve’. To ensure surgeon competency and minimise any ‘learning curve’ effect, ROLARR only includes surgeons who have performed at least 30 rectal cancer resections (minimum of 10 for each procedure). Randomisation also stratifies by surgeon to ensure balance between arms within each surgeon and within the stage that individual surgeons have reached on the learning curve. To be able to statistically assess the learning curve at analysis, data on time-dependent factors known to influence the learning curve will also be collected prior to and on a regular basis during recruitment.

Another issue is blinding. Blinding surgical teams is generally impossible, but blinding patients may be feasible. In ROLARR however, although patients could be initially blinded to their performed surgery, maintaining the blind was felt to be difficult to achieve successfully. ROLARR therefore incorporates objectives measures and central blinded assessments of these measures to reduce potential bias.

Timing of randomisation can also be problematic due to the need for theatre planning. Preferably surgery should take place as soon as possible after randomisation however in ROLARR, up to 28 days after surgery has had
to be permitted. Monitoring timings will take place to allow prompt action on any possible problems that may introduce bias.

Surgical trials are complex to design and implement. Careful consideration needs to be given to the additional issues that arise to ensure an accurate and unbiased interpretation of the results.

A27
NO LARGE DIFFERENCES AMONG CENTERS IN A MULTI-CENTER NEUROSURGICAL CLINICAL TRIAL
Emine O. Bayman, Kathryn Chaloner, Bradley J. Hindman, Michael M. Todd, IHAST investigators
Department of Anesthesia, Department of Biostatistics, Department of Statistics and Actuarial Sciences The University of Iowa, Iowa City, IA, USA

OBJECTIVE: The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a large, international, randomized, partially blinded multi-center clinical trial with a binary outcome (Glasgow Outcome Score = 1 is “good outcome”) comparing intraoperative hypothermia to normothermia. The objective of this study is to quantify the variability among the 30 IHAST centers and to identify centers which were outside of normal variability in the primary outcome. Novel statistical methodology using a Bayesian hierarchical model is used. The standard deviation of the between-center variability in the log odds of a good outcome is proposed as a measure of variability.

METHODS: Bayesian methods for estimation and outlier detection are applied to a hierarchical model assuming log odds of response in each center are different but similar. Analysis was adjusted for treatment, age, gender, and World Federation of Neurological Surgeons score. Graphical and numerical summaries of the between-center standard deviation are examined. The appropriateness of a normal distribution for the between-center variability is examined. RESULTS: In the IHAST, there is center-to-center variation in the log odds of good outcome at each center. The variability is consistent with a normal distribution with posterior standard deviation of 0.504 (95% confidence interval: 0.380 to 0.674). The main effects of all covariates were adjusted for, and no interactions between them were detected. CONCLUSIONS: There are differences between centers, but these differences are consistent with the random variability of a normal distribution with no outlying centers. There was no evidence of a treatment effect either overall or at any one center.

A28
TRIALS IN SURGERY: EVALUATING A SIMPLE OR A COMPLEX INTERVENTION?
Marion K. Campbell, Craig R. Ramsay, Jillian J. Francis
Health Services Research Unit, University of Aberdeen, Aberdeen, UK

When designing a trial, it is important that the intervention being evaluated is clearly specified. In a drug trial, the intervention usually specifies the drug (together with the appropriate dosage) and the action of a patient taking the drug completes the intervention. In surgical trials, the intervention under evaluation is typically described as the direct surgical procedure being undertaken by the surgeon eg laparoscopic fundoplication, inguinal hernia repair, total knee replacement. However, in surgical trials the direct surgical procedure is only one element of the intervention that may affect patient outcome. For example, patient outcome has been shown to be also influenced by the preparation for surgery, the management of the anaesthesia, the expertise of the surgical team and the post-operative rehabilitation regimen. As such, we propose that trials of surgical interventions should be characterised more as trials of complex interventions. The MRC complex intervention framework provides a useful framework for the conceptualisation of surgery as a complex intervention. This perspective suggests that protocols for clinical trials in surgery should become more detailed with greater pre-specification of the elements which might affect outcome (over and above the direct surgical procedure), and greater use of concurrent process evaluation to explore the level of impact of these wider elements on patient outcome. This presentation will present the issues, discuss implications for the design of surgical trials and provide worked examples of how this might be enacted in practice.
A MIXED METHODS STUDY TO ASSESS THE SUCCESS OF BLINDING IN SURGICAL RANDOMISED CONTROLLED TRIALS

Caroline Boulind, Jane Blazeby
Surgical Research Unit, Department of Social Medicine, University of Bristol, Bristol, UK

Background: Blinding is an important feature of randomised controlled trials (RCTs). Meta-epidemiological studies show that lack of blinding can overestimate effect-size by up to 25%. Although many trials now include a blinding protocol they rarely include information about the success of blinding, which is required for appropriate interpretation of trial results. Several methods for the assessment of blinding success are available, but interpretation of these tests can be difficult. This mixed-methods study of a National Institute for Health Research-funded pilot RCT and a Cancer Research UK-funded multi-centre RCT will investigate the success of blinding in these trials and the accuracy of the BBI to assess this.

Methods: Ethics approval has been granted for all parts of this study. To collect the BBI data, patients in both trials are asked to indicate which treatment they believe they received at two time points; day 1 after surgery and the day of discharge prior to unblinding. Research nurses and surgeons (who are also blinded) complete the BBI at discharge. A formula calculates the proportion of un-blinded participants. Following discharge, patients will be interviewed to investigate understanding of blinding and allow more detailed discussion of their answers to the BBI. Surgeons and research nurses will be interviewed to assess their understanding of the blinding process, its implications for RCTs and their views about the blinding process in these trials. The systematic review (SR) includes 115 RCTs assessing surgical interventions. The review will report the percentage of trials reporting tests of blinding success, the methods used and how the results were interpreted. All results from the BBI, interviews and SR will be synthesised to provide a multi-dimensional picture of the role, success and importance of tests for blinding success in surgical RCTs, and the results will be available in April 2011.

ADOPTING NEW SURGICAL DEVICES INTO CLINICAL PRACTICE: CONTRASTING ROLES OF HTA ORGANISATIONS IN CANADA

Sue Ross, Ariel Ducey, Carmen Thompson, Rene Lafreniere, Charles Weijer, Amiram Gafni
Calgary, Alberta; London, Ontario; Hamilton, Ontario; Canada

BACKGROUND: Health technology assessment (HTA) plays an increasingly important part in the adoption of new technologies into clinical practice. HTA provides an independent evaluation of new technologies, including assessment of both effectiveness and cost of new technologies. The HTA process can be considered either as an additional barrier to adopting new technologies, or as a useful integral step in deciding to adopt new technologies. Evidence for this analysis is from a CIHR-funded study examining how ethical and economic principles inform the roles, responsibilities, information and policy needs of stakeholders in the introduction of surgical devices into clinical practice. The research specifically addressed the adoption of new pelvic floor surgical devices into clinical practice.

DESIGN: Our study involves case studies of pelvic floor surgical devices as examples of elective surgeries. In-depth semi-structured interviews were conducted with representatives of relevant stakeholders from clinical, academic and regulatory settings in two Canadian provinces. A variety of HTA organizations were identified, and representatives were interviewed.

OBJECTIVE: To examine the contrasting roles of HTA organizations, and their impact on adoption of new surgical devices into clinical practice.

RESULTS: Preliminary findings suggest that HTA organizations have contrasting and overlapping roles and responsibilities. There are also gaps which result in lack of clear and independent evaluations to guide clinical practice. For example, higher level HTA evaluations are available to recommend types of procedure, but local evaluations are needed to recommend adoption of specific devices. Local evaluations require duplication of effort across institutions.

CONCLUSIONS: Increasing constraints on health care budgets ensure that the role of HTA evaluations is increasingly important in informing the adoption of new surgical devices. HTA organizations must coordinate their activities to ensure their evaluations remain relevant, while avoiding duplication of effort.
RESEARCHERS’ PERCEPTIONS OF ETHICAL CHALLENGES OF CLUSTER RANDOMIZED TRIALS: A QUALITATIVE ANALYSIS

Andrew D. McRae1,2,3, Carol Bennett4, Charles Weijer3, Jamie Brehaut4, Judith Belle Brown5, Allan Donner3, Martin Eccles6, Jeremy Grimshaw4, Raphael Saginur4, Shazia Chaudhry4, Monica Taljaard4

1Division of Emergency Medicine, University of Calgary, Calgary, Canada; 2Rotman Institute of Philosophy, University of Western Ontario, London, Canada; Ottawa Hospital Research Institute, London, Canada; 3Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada; 4Ottawa Hospital Research Institute, Ottawa, Canada; 5Department of Family Medicine, University of Western Ontario, London, Ontario; 6Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Background: Cluster randomized trials (CRTs) pose ethical challenges for investigators and ethics committees. This study examined: 1) How experienced CRT researchers have addressed ethical challenges arising from the CRT design. 2) CRT researchers’ views on the ethics review process. 3) CRT researchers’ views on the need for comprehensive ethics guidelines for CRTs. Methods: Semi-structured interviews were conducted with twenty informants who had been the lead author on two or more published CRTs, or who had authored commentaries on ethical challenges in CRTs, followed by a descriptive qualitative analysis. Results: Informants expressed concern over the logistic feasibility and the potential for bias that may result from a universal requirement to obtain informed consent from research participants in CRTs. Informants suggested that the need for informed consent ought to be related to the type of intervention under study in a CRT. Informants rarely expressed concern regarding the risks to research participants in CRTs, other than risks to privacy. Other important ethical challenges identified in the research ethics literature, including fair subject selection and other justice issues, were not mentioned by informants. Informants expressed the view that variability in ethics review between jurisdictions, and increasingly stringent ethics review in recent years, has hampered their ability to conduct CRTs. The ethics review process has had both positive and negative impacts on CRT conduct. Many informants expressed the view that comprehensive ethics guidelines for CRTs would be helpful to researchers and research ethics committees. Conclusions: Research ethics guidelines for CRTs may be valuable in aiding researchers and research ethics committees. Guidelines should comprehensively address challenges identified by informants in this study, as well as challenges described in the literature that were not identified by informants. These include consent requirements in CRTs, the analysis of harms and benefits, and participant selection and justice issues.

INVESTIGATOR EXPERIENCES WITH THE ETHICS REVIEW PROCESS OF CLUSTER RANDOMIZED TRIALS: AN INTERNATIONAL SURVEY

Shazia Chaudhry, Monica Taljaard, Jamie Brehaut, Jeremy Grimshaw, Martin P. Eccles, Charles Weijer, Andrew D. McRae, Raphael Saginur, Robert Boruch, Merrick Zwarenstein, Allan Donner

2Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital, Ottawa, Ontario, Canada; 2Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada

Background: Cluster randomized trials (CRTs) raise a variety of ethical challenges; yet, there are no comprehensive guidelines for the ethical conduct of CRTs. Variable interpretation by research ethics committees of existing guidelines (which have been developed primarily for individually randomized controlled trials) may have ramifications for the conduct of CRTs. This study investigated the ethics review process of CRTs in health research from the perspectives of investigators conducting these trials. Methods: We implemented an electronic search strategy in Medline to identify CRTs published in English language journals from 2000-2008, randomly sampling 300. A web survey with closed and open-ended questions was administered to corresponding authors of the selected CRTs in a series of six contacts using Dillman’s tailored design method. Trialists surveyed were based in USA/Canada (47%), UK/Ireland (18%), elsewhere in Europe (21%), Australia/New Zealand (5%), and various low/middle income countries (9%). Results: The overall response rate was 64%. Survey respondents were similar to nonrespondents except they were more likely to have accounted for intra-cluster correlation in their analyses (p=0.02). 92% of respondents sought ethics approval for their CRT, approaching a median of 1 ethics committee (inter-quartile range 1-2). The ethics review process had a negative impact on the following aspects of any of their...
CRTs: timely initiation of a trial (26%), feasibility of participant recruitment (15%), scientific validity (11%), and financial cost of conducting a trial (9%). Variability in the ethics review process in multi-jurisdictional trials was experienced by 28% of respondents. 74% (95% CI: 66% to 80%) agreed or strongly agreed that there is a need to develop ethics guidelines for CRTs, and 70% (95% CI: 63% to 77%) that ethics committees could be better informed about distinct ethical issues surrounding CRTs. Final results will be presented by study characteristics, along with a qualitative analysis of open-ended responses.

A33
REPORTING OF RESEARCH ETHICS REVIEW AND INFORMED CONSENT PRACTICES IN CLUSTER RANDOMIZED TRIALS
Monica Taljaard1, Andrew McRae2, Charles Weijer3, Carol Bennett1, Stephanie Dixon3, Julia Taleban2, Zoe Skea4, Jamie Brehaut1, Martin P. Eccles5, Allan Donner3, Raphael Saginur3, Robert Boruch6, Jeremy Grimshaw1
1Ottawa, Ontario, Canada; 2Calgary, Alberta, Canada; 3London, Ontario, Canada; 4Aberdeen, Scotland; 5Newcastle upon Tyne, United Kingdom; 6Philadelphia, PA, USA

Background: Cluster randomized trials (CRTs) present unique ethical challenges. There may be multiple kinds of participants who receive different interventions, e.g., participants at the individual level (patients) and at the cluster level (health professionals); there may also be one or more gatekeepers in charge of each cluster. There are currently no comprehensive ethics guidelines for CRTs, including from whom, when and how informed consent should be sought. We investigated the extent to which authors adhered to two basic requirements of the Helsinki Declaration and the International Committee of Medical Journal Editors, namely reporting of research ethics review and informed consent. We determined whether there has been an improvement over time, and identified characteristics of trials associated with reporting of ethics practices. Methods: We used an electronic search strategy implemented in Medline to identify reports of CRTs published in English language journals from 2000-2008, randomly sampling 300. Two reviewers independently abstracted information from each article. Results: 26% of trials (95% CI 20.7-30.6) failed to report ethics review; the proportion decreased significantly over time. Trials with data collection activities at the individual level were more likely to report ethics review than trials using routine data sources only. Trials accounting for clustering in the design and analysis were more likely to report ethics review. The median impact factor of the journal of publication was higher for trials reporting ethics review. 31.0% of trials (95% CI 25.8-36.2) failed to report consent; the proportion decreased significantly over time. Trials with interventions targeting participants at the individual level were more likely to report consent than those targeting the cluster level. Trials with data collection activities at the individual level were more likely to report consent than those using routine data sources only. Conclusion: Greater clarity in the reporting of ethics practices in CRTs is required.

A34
FACTORS ASSOCIATED WITH REPORTING OF PATIENT CONSENT IN HEALTHCARE CLUSTER RANDOMIZED TRIALS
Andrew D. McRae1,2,3, Monica Taljaard4, Allan Donner3, Charles Weijer2, Carol Bennett4, Zoe Skea5, Jeremy Grimshaw4, Martin P. Eccles
1Division of Emergency Medicine, University of Calgary, Calgary, Canada; 2Rotman Institute of Philosophy, University of Western Ontario, London, Canada Ottawa Hospital Research Institute, London; 3Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada; 4Ottawa Hospital Research Institute, Ottawa, Canada; 5Health Services Research Unit, University of Aberdeen, Aberdeen, UK

Background: Cluster randomized trial (CRT) investigators face challenges in seeking informed consent from cluster members. The interventions may be delivered at the cluster level, thus rendering individual consent meaningless. Identifying and seeking prospective consent from patients may be logistically infeasible due to factors such as cluster size. This study examined associations between reporting of patient consent in healthcare CRTs and inherent characteristics of these trials. Methods: A sample of 161 CRTs conducted in primary care and hospital settings was identified from a random sample CRTs published 2000-2008. Consent practices and study characteristics were recorded by two independent abstractors. Bivariant and multivariable logistic regression analyses were used to examine potential associations between reporting of patient consent and: journal
impact factor, country of study conduct, the year of publication, identification of study as quality improvement, the type of interventions evaluated in the study, the type of interventions used to collect data, and mean cluster size. Results: 86 of 161 studies (53.4%, 95% CI 45.7-61.1%) reported obtaining informed consent from individual patients. Reporting of patient consent was independently associated with: publication later than 2004, smaller cluster size, the evaluation of experimental interventions targeted at patients, and data collection from individual patients. Reporting of patient consent was less likely in trials conducted in lower/middle income countries. Conclusions: Consent practices are associated with the types of interventions used in a CRT. Larger cluster sizes, in which seeking patient consent is logistically challenging, are inversely associated with reporting of patient consent. Publication after the promulgation of UK guidelines for CRTs, as well as secular trends toward more restrictive research ethics practices may explain the association between reporting of consent and publication in later years. Lower impact factor journals should increase efforts to ensure authors comply with international reporting standards for consent practices.

A35
THE LACK OF REPRESENTATIVENESS OF PATIENTS IN RANDOMIZED TRIALS ENDANGER THE SCIENTIFIC BASIS OF EVIDENCE-BASED MEDICINE
Joerg Hasford
Department for Medical Biometry and Epidemiology Ludwig-Maximilians-University Munich Marchioninistr.15 81377 Munich Germany

Evidence-based medicine asks for the use of the best scientific evidence combined with physician’s practical experience and respecting patient’s preferences. Best scientific evidence about therapeutics is provided by randomized clinical trials (RCT). But how representative are the patients admitted to RCTs and the physicians who treat them. Most RCTs aim for the proof of efficacy, i.e. the drug produces a beneficial result under ideal conditions of health care. Thus highly experienced trial physicians of well qualified study centres treat highly selected patients who are thought likely to be very responsive to the new drug, compliant and to be at low risk for adverse drug reactions. Thus typically the majority of patients suffering from the disease under investigation are excluded. In a study done to estimate the proportion of individuals with asthma of a random sample of a community survey, who would have been eligible for one of the 17 major asthma RCTs cited in GINA guidelines, just 4% - 6% of the asthma patients met the eligibiliy criteria. (TraversJ et al, Thorax 2007). Similarly poor results have been reported for other disease areas like osteoporosis and mental disorders too. Thus the results of these trials cannot be generalized to the ‘typical’ patient. The major reason for this unsatifactory situation is the long list of exclusion criteria(e.g. concomitant or prior medication use, medical comorbidities, age), which is so common in trial protocols. The rationale of exclusion criteria and their pro’s and con’s will be discussed. There is little doubt that exclusion criteria should be more carefully discussed in the context of external validity and their impact on the scientific basis of evidence-based medicine.

A36
OPEN VERSUS CLOSED ACCESS TO FULL ACADEMIC TRIAL PROTOCOLS: ADVANTAGES AND DISADVANTAGES
Sue Ross, Laura Magee, Stephen Wood
Calgary, Alberta, Canada; Vancouver, British Columbia, Canada

TRIAL REGISTRATION - The need for registration of academic clinical trials in public access databases (eg ClinicalTrials.gov, ISRCTN) is well established. Some public funding bodies (eg CIHR, NIH, UKMRC) have made registration mandatory for funded trials as part of their governance processes. Trial registration involves abstracting key information, including eligibility, outcome measures and sample size. Registration of trials gives them greater exposure, and should ensure that trial results are more rigorously reported. Investigators have responded to this increasing openness in two ways: publishing the full protocol in a peer-reviewed journal; or, restricting access to protocol details using non-disclosure agreements (NDAs). Each of these approaches had advantages and disadvantages. OPEN ACCESS BY PUBLISHING THE FULL PROTOCOL Advantages: allows access to the full protocol, including complete definitions of primary and other outcomes, which should hold investigators to higher standards of reporting; ensures widespread indexed “registration” of intellectual property; allows open discussion and collaboration; potential sites may volunteer. Disadvantages: research design is widely available and could be plagiarized (this would be identifiable from the published protocol). CLOSED ACCESS USING NDAs
NDAs are legal agreements signed between investigators and potential sites, in which sites agree not to disclose to others any details about the trial. Additional details of the trial are not available without a fully executed NDA. Advantages: no details of the study should leak from potential sites: if they did, legal action could be taken against the source of the leak. Disadvantages: NDAs restrict academic openness by establishing an environment of distrust; prevent open discussion between possible collaborators; provide additional barriers to participating in a trial; may increase bias in reporting results. CONCLUSION - Open access to trial protocols should be encouraged to ensure free and open academic discussion about trials and to reduce biased reporting of results.

A37
ANIMALS, HUMANS, AND THE CONTINUITY OF EVIDENCE: DESIGN AND PRELIMINARY RESULTS OF A SYSTEMATIC STUDY OF CLINICAL TRANSLATION
Jonathan Kimmelman
Biomedical Ethics Unit / Dept Human Genetics, McGill University

Recent systematic reviews of preclinical research show recurrent flaws in the way new therapeutics are validated in animal systems. Yet many of these studies have focused on specific indications (stroke and other central nervous system disorders) and on practices addressing threats to internal validity. In what follows, I will describe the theoretic underpinnings and approach for a presently underway systematic analysis in which experimental designs and outcomes for large cohort of investigational agents will be followed from preclinical studies to randomized trials. Contemplated analyses and preliminary data on our inception cohort of initial published clinical trials will be reported.

A38
HIV PREP: A NEW TOOL FOR PREVENTION, HARM-REDUCTION OR HARM-POTENTIATION?
Madzouka B. Kokolo, D. William Cameron, Dean Fergusson
University of Ottawa, Ottawa, Ontario, Canada

PLAIN LANGUAGE SUMMARY
It might be possible to prevent HIV by taking a pill or an injection of anti-HIV drugs. This concept is called pre-exposure prophylaxis, or PrEP. Although some preliminary studies were promising, we don’t know yet if this actually works in humans. A few large PrEP studies should be completed soon and may provide the answer. However, PrEP research has been very challenging to design and to conduct. Implementing and sustaining PrEP in real-life contexts will surely be at least as difficult. Scientific and lay communities need to figure out how they will deal with upcoming results, in the best interest of people affected by HIV.

ISSUES
Antiretrovirals are currently used to treat acquired HIV infection, to prevent perinatal HIV transmission, and to reduce the likelihood of HIV infection shortly after a high-risk sexual or blood-borne exposure. In some animal studies, HIV antiretrovirals also provided partial protection against infection, when administered before exposure to HIV-like virus. This concept is called pre-exposure prophylaxis (PrEP). Five ongoing clinical studies are testing HIV PrEP efficacy. They should all be completed by 2013, and data are eagerly awaited. However, critical implementation challenges will need to be addressed, if HIV PrEP is proven to work.

DESCRIPTION
Based on previous analyses of methodological and ethical issues in PrEP research, we articulate our discussion around eight areas that we consider particularly relevant: bioethics (design, conduct and dissemination of research); therapeutics (characteristics of PrEP drug regimen); case management (eligibility to and clinical implications of PrEP treatment); psychosocial considerations (personal attitudes and behaviors, social context); health economics (cost-effectiveness, prioritization, coverage); lobbying (HIV treatment versus HIV prevention, accessibility, programming); politics (decision-making process, funding schemes, sustainability); and global equity (United Nations Millennium Development Goals).

LESSONS LEARNED
It will not be enough to find out whether antiretrovirals can prevent HIV. Many multi-level challenges will remain to be overcome to achieve effectiveness in the real world.
RECOMMENDATIONS

More public discussions and multidisciplinary collaboration are needed to optimize community preparedness and appropriate use of data to come.

A39

METRICS FOR EVALUATING SURROGATE ENDPOINTS WITH APPLICATION TO HIV PREVENTION TRIALS

James Dai, James Hughes

Fred Hutchinson Cancer Research Center; Department of Biostatistics, University of Washington, Seattle, WA, USA

Surrogate endpoints are of keen interest in randomized clinical trials. Various statistical metrics have been proposed to evaluate the surrogacy, using data from either a single trial or meta-analysis, e.g., the proportion of treatment effect explained (PTE). One way to assess surrogacy is to examine the correlation between treatment effects on the surrogate and treatment effects on the outcome in multiple trials, using Bayesian models or linear mixed models, though difficulty remains in modeling binary and survival data. In this work we propose a framework to formally test the dose correspondence of two sets of treatment effects, and to provide a new metric that quantifies the variability of treatment effects on the outcome explained by treatment effects on the surrogate. The form of the surrogate and the endpoint can be flexible, encompassing continuous, binary, and time-to-event. The framework can be used in meta-analysis of surrogate endpoints, or a single large trial with heterogeneous treatment effects in subgroups. Data from HIV prevention trials are used to illustrate the utility of the proposed measures.

A40

CAPITALIZING UPON LOCAL CAPACITY AND EXPERIENCE FOR CLINICAL RESEARCH DATA MANAGEMENT IN RESOURCE LIMITING SETTINGS: THE KERICHO CLADE STUDY

Peter Yegon, Rither Langat, Ignatius Kiptoo, Fredrick Sawe, Jonah Maswai, Appolonia Aoko, Margaret Bii, Raphael Langat, Judith Chamberlin, Nicole Close, and Douglas Shaffer

The Kenya Medical Research Institute, Kericho, Kenya

With the growing number of clinical trials conducted in sub-Saharan Africa, the need and obligation exists to develop local capacity and expertise to design, implement and analyze research. Quality data collection, management and analysis is essential for all research. Data collected locally, entered, cleaned and analyzed provides more efficient use of resources and timing for such trials. Through the example of the CLADE study (an unblinded, randomized, prospective, cohort study evaluating the superiority and cost-effectiveness of two Ministry of Health antiretroviral therapy diagnostic approaches), we describe the benefits and challenges of developing this study locally. Steps and decisions throughout the design and execution phase of the research will be described. Components developed include data entry, case report forms, databases, data entry screen design, statistical analysis plans, randomization, data queries, Data Monitoring Committee reports and Quality Assurance plans. Because resources and skills are limited in-country, a mentorship for developing each component was implemented through US based resources at the beginning of the study design phase. In addition, identifying existing local staff with data management experience, Computer Science and programming / statistics skills was critical. Based on local skills, decisions were made on how the data systems were created. For example, as resources and skills was a challenge we decided to use the SQL and Visual Basic programs because the team had experience in both. External staff experienced with data entry and support assisted with local capacity development through mentorship and expert advice before and during execution of the study. Components were developed, reviewed by the mentors, and can now each serve as a template document for future studies. Further, these lessons and templates can now be shared with other local teams engaged in research, with our staff providing mentorship to them.
Background: This trial aims at testing the efficacy of weekly reminder and motivational text messages, compared to usual care in improving adherence the Highly Active Antiretroviral Treatment (HAART) in patients attending a clinic in Yaoundé, Cameroon. Methods and Design: This is a single-centered randomized controlled single-blinded trial. A central computer generated randomization list will be generated using random block sizes. Allocation will be determined by sequentially numbered sealed opaque envelopes. 198 participants will either receive the mobile phone text message (SMS) or usual care. Our hypothesis is that weekly motivational text messages can improve adherence to HAART and other clinical outcomes in the control group by acting as a reminder, a cue to action and opening communication channels. Data will be collected at baseline, three months and six months. A blinded program secretary will send out text messages and record delivery. Our primary outcomes are adherence measured by the visual analogue scale (VAS), self report (SR), and pharmacy refill data (PRD). Our secondary outcomes are clinical: weight, body mass index, opportunistic infections, World Health Organization (WHO) classification, all cause mortality and retention; biological: Cluster Designation 4(CD4) count and viral load; composite: Center for Disease Control (CDC) classification and quality of life. Analysis will be by intention-to-treat. Covariates and subgroups will be taken into account. Discussion: This trial investigates the potential of SMS motivational reminders to improve adherence to HAART in Cameroon. The intervention targets non-adherence due to forgetfulness and other forms of non-adherence. Key words: Adherence, HAART, SMS, text messages, mobile phone, Cameroon, randomized controlled trial Sponsor: Canadian Institutes of Health Research (CIHR) HIV Clinical Trials Network (CTN) international postdoctoral research fellowship award.

Background: High HIV/AIDS prevalence in resource limited communities complicates the conduct of clinical trials in Africa. GCP 4.3.2 requires that investigators inform a subject when care is needed for an intercurrent illness, creating an ethical dilemma when HIV is common, testing is done, but needed care is unavailable. HIV care resources provided by major donor groups allow execution of ethical research by providing necessary care to HIV positive volunteers and can also be strengthened by their clinical trials association. Description: USAMRU-Kenya, a special foreign activity of the Walter Reed Army Institute of Research, has conducted malaria drug and vaccine trials in Kisumu West-Kenya since the 1970s. The first clinical trial to screen study volunteers for HIV was conducted in 2007, and 29% of adult volunteers were HIV positive. This precipitated the ethical need to locally offer comprehensive HIV care and support. PEPFAR funding allowed the district to hire a comprehensive HIV care team that collaborated with the clinical trials teams, ensuring they would have the skills and capacity for managing HIV-positive participants. Ongoing coordination between research and program staff with regular meetings has helped assure the optimal success of both programs. Recommendations: In resource-limited areas with high HIV prevalence, screening volunteers for HIV presents ethical challenges under GCP if those participants cannot access needed care.
medical care. Establishing a strong HIV/AIDS care and treatment program is critical for African sites conducting clinical trials and benefits from a multidisciplinary team approach. With close coordination, both clinical trials sites and HIV-care programs are strengthened by this partnership.

A43

IMPORTANT OF CONFERENCE CALLS FOR COORDINATORS IN MULTI-CENTER CLINICAL TRIALS
Laura Tipton, Meredyth Gehrig, Mary Foulkes
The George Washington University Biostatistics Center, Rockville, MD, USA

Whether they are called nurses, program coordinators, or simply coordinators, the clinical staff members responsible for the day-to-day implementation of a multi-center clinical trial can make or break the trial at that center. These individuals are brought together on a regular basis to review procedures, disseminate new information, and generally troubleshoot to improve the operations of the trial. Since in-person meetings are not always feasible or occur too infrequently to have a consistent impact, conference calls often become the forum for these gatherings.

Conventional wisdom at a data coordinating center for multi-center clinical trials holds that clinics whose coordinators regularly attend routine conference calls are the top performing clinics. Clinic performance is most objectively measured by recruitment volume, drop-out rate, and, where applicable, screen-failure rate. Top performing clinics are defined as those who have high recruitment volume, and for established trials low drop-out rate. Performance was evaluated across multiple multi-center clinical trials coordinated at The Biostatistics Center. In addition to the clinic performance measures described above, coordinator turnover and the presence of multiple coordinators were also evaluated. Data were collected from multiple trials encompassing a range of diseases, study designs, follow-up durations, and funding sources. To reduce the influence of studies with a larger number of clinics, all measures were adjusted for the number of clinics within each trial. Each of these performance measures were compared against conference call attendance over elapsed study time and across a variety of study types. The results challenged that conventional wisdom.

A44

CAN PATIENT DECISION AIDS HELP TRIAL PARTICIPANTS? A NEW APPROACH TO INFORMED CONSENT FOR CLINICAL RESEARCH
Jamie Brehaut, Kelly Carroll, Glyn Elwyn, Raphael Saginur, Kaveh Shojania, Jonathan Kimmelman, Ania Syrowatka, Trang Nguyen, Erica Hoe, Dean Fergusson
Ottawa, Ontario, Canada

Introduction: Current informed consent processes tend to emphasize information provision rather than careful deliberation and decision-making. The International Patient Decision Aids Standards (IPDAS) provide recommendations for working systematically through difficult decisions, such that decision makers will understand outcome probabilities, explicitly weigh benefits and harms, and consider which outcomes they value most. We assessed informed consent documents (ICDs) according to items based on the IPDAS instrument (Elwyn et al. 2009) and, for comparison, items based on current Canadian standards for ICDs.

Methods: 120 ICDs for trials registered with ClinicalTrials.gov were obtained from study investigators. Using a 4-point scale (strongly agree, agree, disagree, strongly disagree), two raters assessed each ICD on 27 items based on current standards for ICDs (Consent items), and 32 IPDAS items. If the mean rating was within the “agree” range, the ICD was said to adhere to that item.

Results: Across all 27 Consent items and 120 ICDs, overall Consent item adherence was 80.8%. Variation in adherence across items was high, ranging from over 95% adherence for 11 items (e.g. ‘ICD included a statement that participation is voluntary’), to 12.5% (‘ICD describes whether investigators/institutions receive compensation’). Across all 32 IPDAS items and 120 ICDs, overall IPDAS item adherence was 33.3%. Only two items showed near-perfect adherence (‘ICD described the advantages of participation’, ‘ICD identified someone to whom questions can be asked’) while 11 items showed adherence rates of less than 5% (e.g. ‘ICDs provide a step-by-step way to decide whether to participate’).
Conclusions: IPDAS standards for good decision-making are generally not adhered to within existing ICDs. We propose that these standards suggest ways to strengthen the validity of claims that decisions about trial participation are informed. Discussion/investigation about which IPDAS components are most relevant to ICDs is warranted.

A45

**MULTIPLE MECHANISMS TO RETAIN PARTICIPANTS IN A LONG-TERM RANDOMIZED CLINICAL TRIAL: THE CAROTID REVASCULARIZATION ENDARTERECTOMY VS. STENTING TRIAL**

Mary E. Longbottom¹, Jason Avery², Jenifer H. Voeks², MeeLee Tom³,
Susan E. Hughes³, Virginia Howard², Alice Sheffet³, Thomas G. Brott¹

¹Mayo Clinic, Jacksonville, FL, USA; ²University of Alabama at Birmingham, Birmingham, AL, USA; ³UMDNJ-New Jersey Medical School, Newark, NJ, USA

BACKGROUND: Successful retention of study participants in long-term clinical trials is essential to avoid costly delays in achieving pre-specified sample size and to maintain adequate study power. Multiple mechanisms to enhance patient retention are required for efficient retention.

METHODS: The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a National Institutes of Health-funded, multicenter, long-term randomized clinical trial, compared the safety and efficacy of carotid stenting to endarterectomy out to four years. The enrollment period was from December 2000 to July 2008. Mechanisms to enhance patient retention included but were not limited to: coordinator training on the informed consent process; site initiation training; patient retention as a standing agenda item at all Principal Investigator and Coordinator meetings; patient handout providing study updates; protocol amendments to discourage and prevent loss- to-follow-up; retention brochure; patient contact cards; partnering with outside agency; tips and techniques in bi-monthly newsletters; requirement for coordinators to obtain a code from the national study Principal Investigator as part of the participant withdrawal process; enrollment reports to sites; and emails sharing successes in retaining participants.

RESULTS: The average age of the cohort was 70 years. The average yearly rate of patient dropout was 6.7% (41 of 610 participants) for 2005, 5.4% (109 of 2022 participants) for 2007, and 6.4% (159 of 2502 participants) for 2009, one year after enrollment completion. Currently in long-term follow-up, dropout rates stand at 7.0% (176 of 2502 participants). This presentation will discuss these rates and the rationale explaining the trial's retention success.

CONCLUSIONS: Attention to patient retention in long-term randomized controlled trials is vital to sustaining study integrity and achieving timely, cost-effective enrollment. Multiple mechanisms to enhance participant retention throughout the study can be effective, thereby retaining adequate study power.

A46

**EFFICIENCY IN OPENING NEW CLINICAL TRIALS VERSUS EFFICIENCY IN ACCRUALS**

Yelena Novick, Aditya Malankar, Nicholas Shuman, Anne Martocci, Lisa Gaynes,
NYU Cancer Institute, Clinical Trials Office NYU Langone Medical Center. New York, NY, USA

Introduction Recent studies clearly indicate that delay in trial activation results in poor accrual statistics. Since 2007 NYUCI has reinvigorated the structure of its clinical trials operations based on the NCI Clinical Trials Working Group recommendations to make activation of investigator initiated clinical trials (IITs) more efficient.

Objective: To evaluate the effects upon accruals and assess the operational efficiency of IITs.

Methods: Assessed accruals and trial characteristics for therapeutic IITs from 07-09. Calculated % accruals to IITs from all therapeutic trials. Compared numbers and %difference between trials that: were newly opened (NwO), accrued (AC), did not accrue (nAC) and the total number open (TO). Calculated %AC from TO. Compared quotients of AC/nAC

Results: There was steady increase in IIT accruals from 07- 09. % accrual to IITs remained >50%. We opened twice the number of trials in 09(13) vs 07(7) and 08(6). There were increases in ACs 07(14) 08(18) and 09(20). The number of nAC remained stable in 07(22) and 08(22); there was a 77% increase in 09 (59). The total num-
bers of TO grew by 11% from 07(36) to 08(40), and by 47% from 08 to 09(59). %ACs were 07-38%, 08-45% and 09-33%. Quotients of accruing trials/non accruing trials were 07(0.6); 08(0.8) and 09 (0.5)

Conclusion: Organizational changes have had a positive impact upon total accruals to IITs and newly opened trials. However that is not synonymous with improvement in the ratio of accruing versus open trials. Analysis of the impact of protocol selection, prioritization, and closing non accruing trials, as well as creation of metrics will provide more exact models to enhance efficiency of the clinical trials process.

A47
HIGH QUALITY RISK MANAGEMENT FOR CLINICAL TRIALS: USE THE DATA AT YOUR HANDS TO MANAGE RISK IN YOUR CLINICAL TRIALS
Jochen Dress, Urs Harnischmacher, Claudia Weiss, Ingrun Leyendecker, Ursula Niewerth, Ursula Paulus
Clinical Trial Center Cologne (BMBF Grant 01KN0706), Cologne, Germany

Quality Risk Management (QRM) offers new opportunities to design effective and efficient processes to assure patient safety and data quality. QRM is a systematic process to handle risks. An example is the combined use of QRM and risk-adapted on-site monitoring. Risk-adapted on-site monitoring is used to selectively adjust the level of monitoring (e.g. selected data is checked, visit intervals are adjusted). To ensure patient safety and data validity even when monitoring is reduced, additional precautions are essential. Thereto, QRM should be used. It allows detecting abnormalities that are not found by on-site monitoring, only. E.g., comprehensive analyses of normally available data can be performed that include all sites and patients. We developed a risk identification and reduction process to support risk-adapted on-site monitoring. A collection of parameters was defined that constitute standard indicators for patient safety and data validity for a multitude of trial types. Processes to generate and analyze these parameters and to trigger interventions were defined. Anomalies of study sites can be detected and action can then be triggered by the process in place and the parameters used. The latter are for instance the number of queries, missings, SAEs, and the time of documentation. Essential additional parameters for patient safety and analyzability of the primary endpoint have to be defined for each trial. The most useful parameters for this are the kind and number of protocol deviations. What constitutes a protocol deviation should be defined in the trial protocol and supplemented in the course of the trial. The described QRM-based measures can be used to ensure patient safety and data validity for a multitude of trial types. They have to be adjusted specifically for each trial according, for instance, to the number of sites, the recruiting rate, and the frequency of on-site monitoring visit to warrant optimal success.

A48
ACTIVE MONITORING OF PATIENT RECRUITMENT IN SURGICAL TRIALS
Inga Rossion, Markus K. Diener, Christoph M. Seiler
Study Center of the German Surgical Society Dept. of General, Visceral and Transplantation Surgery University of Heidelberg Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

Two out of ten multicenter randomized controlled surgical trials of the Study Center of the German Surgical Society have met pre- specified recruitment targets. In general, up to 69 % of randomized controlled trials (RCT) are delayed in recruitment and timely trial termination is jeopardized. Consequently, funding is at risk and clinical relevance of results may be lost. Therefore, active management is essential to avoid poor recruitment. We describe tools for monitoring of recruitment and possible benefits.

Using indicators for trial progression (initiation of centers, screening lists, recruitment curves and rates) deviations may be explored. Actual recruitment patterns of investigator initiated surgical trials are described and compared with planned trial course (10 trials, >110 participating centers, >2.000 randomized patients). Factors of influence are identified and consequent actions taken to improve patient recruitment are discussed (initiating new participating centers, closing centers with bad performance, active screening of patients, advertising the trial among investigators or patients, correcting eligibility criteria, prolonging recruitment time, changing other design issues).

When planning clinical trials in surgery, potential factors influencing patient recruitment must be identified and their potential impact assessed thus rendering possible to predict realistic recruitment patterns. A well defined
A recruiting strategy should be put in place allowing for continuous monitoring of key indicators. Prompt reaction and active correction of recruitment course is needed. Having a portfolio of predetermined compensating measures at disposal will prevent substantial loss of time thus allowing adaption of recruitment goals and termination of trials within acceptable time limits.

A49
AN EXAMINATION OF SITE VISIT DATA AUDIT RESULTS COMPILED DURING THE INITIAL FOUR YEARS OF A LONG-TERM CLINICAL TRIAL
Wendy L. McBee¹, Traci E. Clemons³, Emily Y. Chew², John Paul SanGiovanni²
¹The EMMES Corporation, Rockville, MD, USA; ²National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Considerable expense may be incurred to ensure data integrity in a long-term clinical trial. A most significant expenditure for a Sponsor is the conduct of in-person site monitoring visits and data audits at each data collection site. Eighty-two clinical sites participating in the Age-Related Eye Disease Study 2 (AREDS2) are tasked with following approximately 4,000 participants throughout five years of follow-up. Data pertaining to effects of supplemental doses of xanthophylls and omega-3 fatty acids on the progression of age-related macular degeneration and moderate vision loss, among other things, are collected at annual visits and semi-annual telephone contacts. The AREDS2 Coordinating Center employs Protocol Monitors who visit each AREDS2 clinical site on a regular basis and follow a standardized procedure for conduct of the visit. A data audit of fields pre-determined by the Sponsor and statisticians to be key to the outcome data is a necessary component of the visit. The Monitor compares data entered into the study database to that identified as source by the clinical site. An error proportion provided as the number of errors per 1,000 fields is calculated. Each clinical site has had more than one data audit at this stage of the study. An examination of the audit results will be reviewed. This review will compare error rates between time points, examine the case report forms producing the highest error rates, look at the types of errors being made (e.g., keystrokes versus transcription mistakes), evaluate the impact of new clinical site staff on data audit results, and determine if the Monitors performing the data audits are calculating a similar number of elevated error rates. The perceived impact of data audit results on data integrity and any strategies for improvement, if applicable, will be provided.

A50
SYSTEMATIC REVIEW OF THE METHODS AND EFFECTS OF SOURCE DATA VERIFICATION IN CLINICAL RESEARCH
Roxanne Ward, Dean Fergusson
Children’s Hospital of Eastern Ontario Clinical Research Unit, Ottawa, Ontario, Canada; The Ottawa Hospital Research Institute Clinical Epidemiology Program, Methods Centre, Ottawa, Ontario, Canada

Background: Good Clinical Practice (GCP) Guidelines were established in 1996 and describes the responsibilities of all participants in the conduct of a clinical trial. These guidelines state that clinical trials should be adequately monitored to ensure that the data are complete, accurate and verifiable. Source data verification is conducted as part of monitoring to compare data collected at the source to that which is recorded on a case report form and is the only method to guarantee that data are complete, accurate and verifiable. However, GCP Guidelines are vague and lack evidence as to the degree of source data verification required and whether or not source data verification affects study outcomes. Objectives: The primary objective of this systematic review is to establish the evidence base for source data verification; specifically to examine published methods of source data verification and examine the effect of source data verification on study outcomes. Methods: Using an explicit search strategy we searched Pubmed, EMBASE and The Cochrane Library for all studies, guidelines and reports where a method of source data verification was documented and evaluated or that reported on the effect of source data verification on study outcomes (including non-English articles). Two content experts independently conducted the initial screening; consensus was achieved, followed by subsequent reviews. Hand searching of titles will be conducted in relevant journals in addition to reference lists of relevant studies, web sites of clinical trial associations, research groups, and conference proceedings of clinical trial organizations. Results: There were 653 articles for the initial screening. Subsequently, 73 were included; 10 were comparative or clinical studies, and the remaining were reviews or reports. Significance: We will synthesize the evidence from the search strategy and hand searching to identify methods of source data verification and reported impact on study outcomes.
A51

FOSTERING TRANSLATIONAL RESEARCH AT AN ACADEMIC MEDICAL CENTER
Dorothee Arenz, Muriel Freudenberger, Vera Ossendorf, Jens Brüning, Thomas Benzing, Oliver A. Cornely

Clinical Trials Center Cologne, University of Cologne, Cologne, Germany; Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

Objective: To establish an effective and traceable gateway between basic and clinical research at the University of Cologne. Background: Basic scientists are increasingly requested to translate their results into clinical application. Likewise clinicians should identify unmet medical needs and initiate targeted basic science research. Although the idea of translation is generally agreed on, it is a bottleneck in medical research.

At academic medical centers the complete scope from basic research to clinical evaluation is available on the same campus, seemingly creating the perfect environment for successful translation of research developments. Still, the number of projects originating from the university’s labs and being evaluated at its hospital is small. ZKS Köln and CECAD did set up a navigation program to foster translational medicine.

Methods: At the University of Cologne each of the two entities employed a navigator. Navigator 1 is a cell biologist with a focus on genetics and pharmacology, who is an experienced clinical trials manager, too. Navigator 2 is double trained as a nurse and as a pharmacist, with a focus on clinical trial management and regulatory affairs of drug licensing and medical products. Our navigator tandem counsels basic scientists and clinician researchers on where to find a complementary partner, how to direct research towards a clinical application, and where to apply for funding.

Results: We identified 25 basic science researchers deemed capable of making clinically relevant discoveries. 1 month after initiating navigator counseling 7 translational projects have been created. Of these, 4 target drug use, and 3 medicinal products. Funding has been generated for a first project linking an animal model with a clinical disease.

Conclusion: The navigators appear to enable a time efficient and visible transfer from basic to clinical research, and may have the potential to enhance the impact of the university on unmet medical needs.

A52

AN ORGANIZATIONAL STRUCTURE TO MANAGE ANALYSES AND MANUSCRIPT DEVELOPMENT IN THE HEPATITIS C ANTIVIRAL LONG-TERM TREATMENT AGAINST CIRRHOSIS (HALT-C) TRIAL
Kristin K. Snow, Anne M. Stoddard, Teresa M. Curto, Margaret C. Bell

New England Research Institutes, Watertown, MA, USA

In a multi-center clinical trial, dissemination of key results must be accomplished in a timely fashion. The Data Coordinating Center (DCC) must prioritize competing analysis requests and support writing group interactions, while rationing limited analytical resources across the diverse research interests of the investigators.

The National Institutes of Health-sponsored HALT-C Trial was a multi-center randomized, controlled trial in 1050 patients with chronic hepatitis C and advanced fibrosis conducted through 10 clinical centers, a central virology laboratory, and a DCC. HALT-C included lead-in, randomized, and observational followup phases and 39 approved ancillary studies. Here we describe the procedures used by the DCC to facilitate the publication process.

The DCC collaborated with investigators to review, approve, and rank manuscript proposals into 9 priority levels. The DCC conducted data analyses in rank-order and managed the publications from manuscript concept through journal submission stages. Steps included:

(1) Equitable assignment of investigators to focused writing groups, (2) Assignment of statistician or statistical team, (3) Development of statistical analysis plan, (4) Monthly calls of active writing groups, (5) Completion of statistical analyses, (6) Lead author assignment of writing tasks, (7) Regular status reports to investigators, (8) Quality control review of analyses by a second statistician, (9) Investigator peer-review of manuscripts prior to journal submission.

The DCC tracked progress of manuscript proposals from analytic start to journal publication to determine timelines. This process was effective in forecasting DCC capacity and resource allocation within budget constraints.
To date, 55 papers have been published or accepted in high-quality journals and 25 manuscripts are in draft or submission stages.

**A53**

**PROJECT MANAGERS ARE WORTH THEIR WEIGHT IN GOLD**

Tilly Yau, Nicole C. Close  
EmpiriStat, Inc., Mt. Airy, MD, USA

Whether you are building an opulent Las Vegas Casino, developing the infrastructure of a small Contract Research Organization, or structuring your Clinical Development Program, the benefits of having Project Management are priceless. Clinical trial organization, staffing and budgets are often void of the Project Manager (PM) role, and the responsibilities of a PM are delegated or distributed among the existing team members, often leading to inefficiencies and a lack of resources. Being an effective PM is about having a myriad of knowledge and skills, and the ability to communicate seamlessly across project functions with varying levels of involvement. When it comes to Clinical Trial Development and Management, Project Management is crucial to move the trial forward, from Phase I and ultimately to a New Drug Application. Why are PMs worth their weight in gold? The PM is responsible for fostering team participation, creating a team contract, defining the Project Charter and scope, setting project boundaries, delegating tasks, making key recommendations on who should be included on the team, developing the deliverable schedule, estimating and monitoring staff effort and spending, providing risk assessment, creating counter measures to reduce risk, managing changes to the plan and providing continuous team, Sponsor and stake holder communication. Through a case example of a clinical trial, the inclusion and exclusion of a PM will be demonstrated with the associated benefits and potential considerations. At the conclusion, we will discuss the qualities that a PM should have including those soft skills as grace under pressure, willingness to be accountable, and the motivational skills to keep the team moving forward often under very tight deadlines.

**A54**

**THE DELICATE BALANCE BETWEEN INDEPENDENCE AND COLLABORATION: PERSPECTIVES FROM ACADEMIC AND INDUSTRY STATISTICIANS**

Chao-Yin Chen1, Robin Bechhofer2, Jan Feyzi2, Kurt Olson1  
1Global Biostatistics, Amgen Inc.; 2Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison

The independent statistical group (ISG) plays an essential role in monitoring the accumulating safety and efficacy information in ongoing clinical trials. Over the course of the trial, the ISG supports the data and safety monitoring committee (DMC) by performing analyses of unblinded data while maintaining its independence from both the sponsor and the study steering committee. The responsibility of the ISG to the DMC is fulfilled as the data monitoring activities end. The experience and knowledge that the ISG has acquired from analyzing the ongoing trial data can provide valuable insight when planning for the final analysis.

This will be a joint presentation by representatives from an ISG and sponsor. The process of collaboration that was used in planning for, and executing, the final analysis of a recently-completed large outcomes trial will be described. Topics to be covered include 1) mechanisms implemented to ensure that such collaboration would not impact the integrity of the trial and would maintain the blind prior to the final database lock; 2) relative roles and responsibilities of the two statistical groups during this period; 3) the timing and process of interactions leading up to the final analysis, 4) lessons learned from our experiences, and 5) recommendations of best practices for this type of collaboration.
A55  EVALUATION OF MASKING SUCCESS OF SHAM OCULAR INJECTIONS
Adam R. Glassman for the Diabetic Retinopathy Clinical Research Network (DRCR.net)
Jaeb Center for Health Research, Tampa, FL United States. Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14269, EY14229.

Purpose: To evaluate the success of masking study participants to treatment allocation using sham ocular injections in a DRCR.net multicenter randomized trial.

Methods: Participants with one study eye were randomized to: prompt laser plus (1) sham injections as needed every 4 weeks, (2) intraocular ranibizumab injections as needed every 4 weeks, or (3) intraocular triamcinolone injections as needed every 16 weeks with sham injections as needed every 4 weeks; or (4) deferred laser with intraocular ranibizumab injections as often as every 4 weeks. Participants with 2 study eyes were randomized to sham+laser in one eye and one of the other 3 treatments in the other eye. Sham injections were used to mask injections, while there was no masking of laser treatment. The procedure for all injections was the same. For sham injections, the syringe hub without a needle was pressed against the eye. At 1 year, each participant guessed whether the injections received were real, sham, or sometimes real/sometimes sham.

Results: Among 423 participants with one study eye, the correct assignment was stated by 10% of the sham group (meaning 90% thought they received real injections), 88% of the ranibizumab+prompt laser group, 90% of the unmasked ranibizumab+deferred laser group, and 44% of the triamcinolone group. Among the 112 participants with 2 study eyes, the correct assignment was stated for 84% of the ranibizumab+prompt laser eyes, 88% of the ranibizumab+deferred laser eyes, and 31% of the triamcinolone eyes, while the correct assignment was stated for 24% of the sham eyes.

Conclusions: Successful masking of an intraocular injection can be accomplished when a detailed procedure is followed which carefully mimics a true injection procedure. Masking appears less successful when one eye receives real injections and the other eye receives sham injections or an individual eye receives both real and sham injections.

A56  BLINDING IN RANDOMIZED BEHAVIORAL CLINICAL TRIALS
Elizabeth Avery, Imke Janssen, Molly Martin, Tamara Olinger, Steven Rothschild
Department of Preventive Medicine, Rush University Medical Center, Chicago, IL, USA

Double-blinding is a basic tenet of clinical trials. Randomized behavioral clinical trials present unique challenges in the design and logistics of blinding. Treatment arms are distinct and participants know to which arm they have been assigned based on the description given during consent. This limits the participant blind. Over the last decade, the Department of Preventive Medicine at Rush University Medical Center has conducted numerous behavioral clinical trials within which strategies for maximizing blinding to ensure rigorous study design have been implemented. The goal of this presentation is to review approaches to maximizing blinding in a behavioral trial: 1. Investigators must communicate their belief in equipoise with regard to study design to recruiters. Recruiters must internally communicate that same belief when describing the study to participants. When all trial personnel and participants believe no treatment is superior to another, differential dropout can avoided; 2. Complete separation between outcomes collection staff and the intervention staff is needed to ensure unbiased outcomes ascertainment; 3. Most investigators, all recruiters and outcomes collection staff should be blinded to research hypotheses under investigation; 4. A priori some investigator(s) may need to be un-blinded to treatment assignment to overseeing the implementation of the behavioral interventions. All other investigators should be blinded to treatment assignment; 5. Limit the number of data managers and statisticians who have full access to the data and know the participant’s treatment assignment, outcomes, and intervention progress; and 6. The data safety monitoring committee is usually kept blinded unless they ask to be un-blinded to fulfill their directive. Using these research strategies has resulted in greater rigor in our implementation of randomized behavioral clinical trials.
Diagnostic multi-reader, multi-case studies describe, measure, and test the diagnostic accuracy of a medical device. Unlike traditional clinical study designs where patients are randomly assigned to one of two or more treatment groups, often patients in these studies are evaluated by multiple diagnostic modalities and interpreted by multiple readers. Randomization in selection and order of interpretation plays an important role in the successful design and implementation of reader diagnostic studies by reducing potential sources of bias.

Reader studies present unique logistical challenges in study design, which can be addressed with randomization. Two separate and equally important components of these studies are the acquisition and the interpretations, or readings, of the cases. Generally these studies have access to more negative potential cases than positive cases. It would be costly and inefficient to include all the available negative cases during interpretation. To reduce bias in the selection, negative cases must be randomly selected, and may be randomly selected within strata to reflect a particular distribution of the population characteristics.

To prevent reader fatigue during image interpretation, cases are often split into small subsets to be read over several sessions. Assigning cases to sets must be random and the sets should include a similar proportion of positive and negative cases. Interpretations of the same cases using different modalities must be performed on separate days, usually after a washout period. The order in which the cases are presented to the readers must also be random, and preferably unique to each reader.

We will discuss several fully crossed multi-reader multi-case studies with non-sequential interpretations. We will describe how randomization and random allocation were used to reduce bias; provide examples of how randomization and random allocation were implemented during these studies, and suggest strategies for including randomization during the planning phases of future studies.

When should RCTs standardize co-interventions?

In many critical conditions, such as cardiac arrest, TBI, or stroke, the acute clinical management of these patients varies widely from clinic to clinic and even from clinician to clinician. Some large, unblinded Phase III multicenter clinical trials to evaluate new treatments (particularly surgical or procedural) for these conditions have failed because of their inability to detect the experimental treatment signal in the presence of multiple, unequally applied co-interventions. For example, to date, not a single phase III clinical trial in traumatic brain injury (TBI) has shown a positive result, leaving patients with no treatment for this devastating condition. Although the reasons are complex, one prevailing concern is that the wide variation in outcome has resulted in washing out the treatment effect. Therefore, some trials now attempt to standardize the co-interventions by mandating the study investigators adherence to certain clinical protocols which may not be consistent with their personal or their clinic’s standard of care. On one hand, such standardization helps control co-intervention variability and consequently helps both to minimize the sample size and to generate an unambiguous study result. On the other hand, having to change the standard of care could be a disincentive to clinical investigators, and the amount of data that must be collected to ensure compliance with the standardized co-intervention protocol could be a large and costly burden on the study. Finally, are we compromising the generalizability of the treatment effect by standardizing all co-interventions? We will compare some of the trials that did and did not standardize co-interventions; present our experience of a currently ongoing Phase III trial of TBI; and will discuss impact on the statistical inference and data management.
A59
SUICIDE RISK IN SUBSTANCE ABUSE TREATMENT CLINICAL TRIALS, IS ADVERSE EVENT REPORTING ALONE SUFFICIENT?
Robert Lindblad, Paul Van Veldhuisen, Maria Campanella, Radhika Kondapaka, Steve Sparenborg, Carmen Rosa
Rockville, MD; Bethesda, MD, USA

Adverse Event (AE) reporting is the standard assessment tool to ensure the safety of subjects enrolled in clinical trials. The National Drug Abuse Treatment Clinical Trials Network (CTN), established by the National Institute on Drug Abuse (NIDA), has completed 24 randomized clinical trials all of which used adverse event reporting to assess safety. Two completed clinical trials enrolling 480 subjects, 225 in substance abuse and 255 in ADHD/smoking, that employed standard AE reporting strategies and the Beck Depression Inventory (BDI), were analyzed using data from the publically-available CTN data share website. Of 480 subjects enrolled, no cases of successful suicide were reported. Adverse event reporting captured 4 (0.8%) subjects with events related to suicide based on MedDRA preferred terms of depression suicidal (n=1), suicidal ideation (n=2) and suicide attempt (n=1). Three of these four events (75%) were captured on the BDI. One question on the BDI addresses suicidal thoughts or wishes, with 2 of the possible responses as: I have thoughts of killing myself, but I would not carry them out (no intent) and I would like to kill myself (intent). Using baseline and follow-up assessments, response to no intent occurred in 82 (17.1%) of subjects and in 3 (0.6%) with intent. Only 3 of 85 subjects (3.5%) identified by the BDI were enrolled in the substance abuse clinical trial, 70 out of 85 events (82.4%). Relying on AE reporting alone can grossly underestimate the suicide risk in clinical trials and especially substance abuse trials. Combining AE reporting with a standardized assessment tool provides improved safety surveillance in the vulnerable population enrolled in substance abuse clinical trials.

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A60
ADVERSE EVENT SIGNAL DETECTION: OVERALL COMPARISONS, FUTURE PROJECTIONS AND FALSE DISCOVERIES
Jing Huang, Julie Ma and Jitendra Ganju
Amgen Inc, San Francisco, CA, USA

One challenge with detecting signals from unexpected adverse events (AEs) in randomized clinical trials is the high rate of false positive findings if the per comparison error rate is controlled, or the high rate of false negative findings if the family-wise error rate is controlled. A different matter is evaluating, after the trial is completed, whether the assessment of risk changes if the trial period is increased (i.e. either a longer treatment period or a prolonged observation period). We propose a method, intended for informal inference, to address the dual topics of high error rates and risk assessment under trial extension. The method is applied to two real data sets. Limitations of the method are also discussed. The following is proposed: (a) visualization of AE data to help decide whether or not to proceed with additional analyses. (b) If further analysis is suggested, then for each AE, make future projections of the number of subjects with that AE based on a weighting scheme using empirical Bayes methodology. (c) Flag AEs that are deemed significant based on overall incidence from the observed and projected portions of the trial after controlling the false discovery rate rather than a family-wise error rate. The new AEs flagged by extending the trial are additional AEs to pay attention to in making the overall risk assessment.
A61
RISK OF DEATH WITH APROTININ IN CARDIAC SURGERY: A BAYESIAN EVIDENCE SYNTHESIS OF RANDOMIZED AND OBSERVATIONAL STUDIES
Brian Hutton, Lawrence Joseph, Dean Fergusson, Stan Shapiro, David Mazer
McGill University, Montreal, Canada

Background: Inclusion of observational studies in meta-analysis with randomized controlled trials (RCT) is a debated practice. Given past conflicts regarding the safety of aprotinin in cardiac surgery from different study designs, an advanced approach to synthesize all evidence is of interest.

Objective: To estimate bias-adjusted meta-analyses of mortality for aprotinin compared to tranexamic acid (TXA), aminocaproic acid (ACA), and no treatment using both RCTs and observational studies, and to assess the comparability of these estimates relative to meta-analyses of RCTs.

Methods: We searched Medline, Embase, and the Cochrane Database. A three-stage approach to meta-analysis was pursued: Stage 1- meta-analysis of RCTs only, and RCTs and observational studies together; Stage 2- meta-regression analyses of RCTs and observational studies; and Stage 3- meta-regression analyses of RCTs and observational studies coupled with bias adjustment at the study level. All meta-analyses used a Bayesian hierarchical approach, and bias adjustments of observational studies were derived from a clinical expert.

Results: Totals of 77, 26 and 12 studies were available for comparisons of aprotinin with no therapy, TXA, and ACA, respectively. Using these alternatives as reference groups for assessments versus aprotinin, comparisons of mortality based on RCTs alone resulted in estimated odds ratios of 0.92 (95% CrI 0.64-1.33), 1.45 (0.62-3.54), and 1.68 (0.23-25.40), while inclusion of observational evidence modified estimates to 1.16 (0.82-1.59), 1.35 (0.99-1.85), and 1.93 (1.18-3.24). Multivariate meta-regression further changed estimates to 0.82 (0.33-1.76), 1.28 (0.52-2.79), and 1.67 (1.07-2.98), while incorporation of bias adjustments produced final estimates of 0.77 (0.29-1.51), 1.24 (0.47-2.73), and 1.67 (1.05-3.06).

Conclusions: Pooled estimates suggested that aprotinin is associated with an increased mortality risk compared to ACA, while comparisons with TXA and no therapy are inconclusive. Inclusion of observational studies reduced uncertainty, while bias adjustments had a minimal impact on point estimates and mildly widened credible intervals

A62
A NEW TOOL FOR FLAGGING ADVERSE EVENTS OF POTENTIAL CLINICAL INTEREST
David Kerr, Axio Research
Seattle, WA, USA

There are many instances where reports are produced of dictionary-coded adverse events (AEs) cross-tabulated by treatment arm and these reports are perused visually for treatment differences. To speed this process, many times the computer programs which create these reports affix p-values for the comparisons and sometimes p-values below a certain threshold (e.g. 0.05) are specifically flagged. Many times, however, particularly for events with relatively small event counts, the results will not necessarily be statistically significant but nonetheless are still worthy of review from a clinical standpoint. For example, an imbalance of 6 vs. 1 for patients with a heart attack would not necessarily have a p-value below 0.05, but may well cross a threshold which would warrant further review by a clinical reviewer.

To aid in flagging AEs for clinical review, a new statistic (the Kerr statistic ) was developed. It utilizes both the p-value of the comparison as well as the magnitude of the difference. In its simplest form, the Kerr statistic is defined as:

$$\log_{10}(p\text{-value}) + \text{abs}(\log_{10}(\text{odds ratio}))$$

The clinical reviewer can set the level of sensitivity that is used for each review. Values > 1.60 show at least a minimum amount of trend; values > 1.75 show a large trend, even if not necessarily borne out by a traditional test of statistical significance. The Kerr statistic has good properties that go beyond those that would be found using solely the p-value and is a useful tool for quick filtering of a possibly lengthy report so that clinical reviewers can see events that would potentially warrant further investigation, although it is important to remind the clinician reviewer that statistical inferences from this table are not valid.
A63
CLUSTER RANDOMIZATION OF TEST AND CARE SITES IN THE TLC-PLUS TRIAL
Deborah Donnell, Geetha Beauchamp, Ting-Yuan Liu
Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle WA, USA

The TLC-Plus trial (HPTN065) is evaluating the feasibility of increasing uptake of HIV testing, linkage to care and adherence of antiretroviral therapy in two communities in the US: The Bronx, NY and Washington DC. Two components of the trial use a cluster randomized design to test the use of financial incentives compared to the existing standard of care. The strategies are being implemented at each of 20 facilities in the Bronx and Washington DC, with 20 (10 in each city) randomized to each condition. Baseline data on trial outcomes and relative patient volume was used to design and select a randomization. The algorithm to select a randomization was required to be balanced with respect to two baseline characteristics. Both baseline characteristics had high variability between sites at baseline, and in addition a post-hoc addition of randomization in blocks was added. Four strategies for randomization are compared for this cluster randomized trial with relatively few clusters: completely random, matched pair, restricted randomization and propensity score matching. We compare the relative strengths of the restricted randomization strategy compared to other strategies. Three aspects are of particular interest: the robustness of the randomization if baseline propensity is a poor predictor of outcome propensity; the impact of randomization strategy on the power of the study; and the impact of the blocking on the design of the study.

A64
FUTILITY TRIALS IN NEUROLOGY REVISITED
Barbara C. Tilley, Jordan Elm, Sheng Luo, Karl Kieburtz, Jay Herson
University of Texas School of Public Health, Biostatistics, Houston, TX, USA; University of Rochester, School of Medicine and Dentistry, Rochester, NY, USA; Johns Hopkins University, Department of Biostatistics, Baltimore, MD, USA

Phase II futility trials based on the design of early Phase II trials in cancer have been used in stroke, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS). The goal of a futility trial is to eliminate potentially futile treatments using a design that requires a smaller sample size than required for a confirmatory, Phase III trial. Only those treatments that cannot be shown to be futile proceed to Phase III. Various designs have been used. The NINDS IMS futility trial in stroke used an historical control and a binary outcome. In NET-PD futility trials, four potential treatments for Parkinson’s disease were evaluated. Two small placebo groups were included as calibration controls, but futility comparisons were made to an historical control rate of change in the Unified Parkinson’s disease rating scale (UPDRS) from the DATATOP trial. The observed calibration control rates of change were much less than the historical rate of change from the placebo group in DATATOP. Adjustments were made to the futility threshold derived from DATATOP and only one treatment was carried forward to Phase III. Given the uncertainty regarding rate of UPDRS change in PD, a more recent NET-PD futility study was designed with a concurrent control. In ALS, a dose selection design was followed by a futility study with comparison made to a concurrent control. In that design a bias correction was introduced to adjust the use of data from the selection design in the futility comparison. In current cancer trials a Bayesian approach to Phase II trials is generally used. We will compare the different approaches to futility trials in neurology and in cancer, discuss options for future Phase II futility trials in neurology, and discuss possible applications outside of neurology and cancer.

A65
OUTCOME CHOICE IN THE DESIGN OF CLINICAL TRIALS FOR THE ELDERLY
Michael E. Miller, Walter T. Ambrosius, Fang-Chi Hsu, Dan Beavers, Mark A. Espeland
Department of Biostatistical Sciences Wake Forest University School of Medicine Winston-Salem, NC, USA

Clinical trials in the elderly often target interventions for the prevention, rehabilitation, or reduction in the overall burden of a specific disease/impairment. These separate aims have different implications for the choice of primary outcomes, eligibility requirements, frequency of outcome ascertainment and statistical approaches. Furthermore, eligibility and outcome decisions can influence the choice of statistical methods. Trade-offs must be made between time-to-event and repeated measures approaches, and both short- and longer-term outcomes should be considered. This talk will use the NIA-funded Lifestyle Interventions and Independence for Elders (LIFE) Study (N=1600; 8 sites) as an example of how the choice of a prevention hypothesis and a bidirectional primary
outcome of mobility disability critically influenced trial design. Discussion of trial design will focus on the frequency of outcome ascertainment, the role that missing outcomes play in selection of the primary outcome, and the potential trade-offs between outcome selection and the number of statistical assumptions that are necessary to address the primary hypothesis. We recommend that for such trials, intervention effects should be captured by simple, repeatable primary outcomes that minimize the breadth of required statistical assumptions.

A66
THE STAR TRIAL: CAN QUALITY OF LIFE BENEFIT OFFSET ANY SURVIVAL DETRIMENT?
Fiona Collinson, Christopher McCabe, Janet Brown, Julia Brown, Helen Howard, Walter Gregory
University of Leeds, Leeds, UK

STAR is an NIHR HTA-funded UK randomized phase II/III study of first-line sunitinib in metastatic/locally advanced clear cell renal carcinoma (mRCC). It compares the utilization of a conventional continuation strategy (CCS) with an experimental drug-free interval strategy (DFIS). Convention dictates sunitinib is continued until progression or unacceptable toxicity. However a DFIS has the potential advantage of improved quality of life (QoL) and cost-effectiveness, due to longer time-periods off-treatment, as well as potentially delaying onset of drug resistance. The trial is unique in determining whether QoL benefits from DFIS can offset any detriment in overall survival (OS). Endpoints will assess both survival and QoL separately, but will also assess QALY (quality of life year gained). Minimal data is available to power on a QALY outcome. The QALY data from the phase II part of the trial will therefore be used to inform and verify the powering of the overall phase III trial. The multi-stage design maximizes resource efficacy by facilitating a seamless transition between the phase II and III parts, assuming attainment of the phase II endpoints (recruitment rate and time to strategy failure). Novel outcome measures (time to strategy failure and summative progression free interval) have also been required, due to the intermittent nature of the drug free interval strategy. A tissue and imaging predictive biomarker substudy is planned; aiming to identify ways of predicting benefit from sunitinib and appropriate treatment strategy at an earlier timepoint. A qualitative substudy to explore patient feelings regarding trial entry and stopping treatment will inform recruitment strategies in phase III. The STAR trial will be an exemplar trial in the evaluation of optimal treatment strategies for targeted therapies in other diseases. We will discuss the methodology relating to the novel endpoints in this study, and discuss implications for future trial design.

A67
POTENTIAL DANGERS OF INAPPROPRIATE FUTILITY BOUNDARIES
Susanne May1, Andrea Cook2, Daniel Gillen3, Graham Nichol1, Scott Emerson1
1University of Washington, Seattle, WA, USA; 2Group Health Research Institute, Seattle, WA, USA; 3University of California, Irvine, CA, USA

Background: Group sequential trials include periodic assessments for a number of reasons. One is to determine whether interim results provide sufficient evidence of either benefit or harm to suggest that the primary study question has been answered. Another reason is to check whether the study is unlikely to show the hypothesized benefit even if the maximum sample size is achieved (futility). If interim results are presented on a test statistic scale and no confidence intervals are presented, a statistically significant harmful effect might be missed. This is of particular relevance in trials that are performed under exception from informed consent for emergency research, because regulation 21 CFR §50.24 of the Food and Drug Administration mandates that there be evidence to support the potential of a direct benefit to enrolled subjects. Objective: To compare the appropriateness of futility boundaries for monitoring clinical trials with particular focus on studies conducted under exception from informed consent. Results: We compare the characteristics of a variety of futility boundaries (including O'Brien-Fleming and Emerson-Fleming boundaries) and discuss their acceptability, advantages and disadvantages. We present an example of a Data Safety Monitoring Board (DSMB) approved sequential study design that was conceptualized based on Z statistics, but later revised by the same DSMB when the full inferential properties were considered. Conclusions: For group sequential clinical trials, some popular options for futility boundaries might represent inappropriate choices for monitoring. Specifically, options for futility boundaries should have a lower bound such that a trial will be stopped if a statistically significant harmful effect is observed.
A68
COMPARISON OF FUTILITY MONITORING METHODS USING RTOG CLINICAL TRIALS
Qiang Zhang¹, Boris Freidlin², Edward L Korn², James J. Dignam¹
¹Radiation Therapy Oncology Group, American College of Radiology, Philadelphia, PA, USA;
²Biometric Research Branch, National Cancer Institute, Bethesda, MD, USA

Futility monitoring is an important component in the conduct of clinical trials. An optimal rule would allow timely stopping if the new therapy is harmful or is unlikely to ultimately prove effective. Methods proposed for futility monitoring include unadjusted 95% confidence intervals (CI), repeated CI (RCI, adjusted for multiple looks), testing alternative hypothesis with small alpha (0.0025), conditional power (CP) bounds, and the linear 20% inefficacy boundary (LIB20) (Freidlin, Korn, and Gray 2010). We evaluated the performance of these methods relative to having no futility boundary, using event histories from completed clinical trials of the Radiation Therapy Oncology Group.

Among sixteen trial-arm comparisons from different disease sites considered 9 trials that were clearly negative were identified. Total sample size and information for each negative trial were calculated using protocol specified effect size, type I, and type II error rates. Interim test statistics were reconstructed for each of the three proposed futility analysis schedules. Operating characteristics of the futility monitoring rules under three analysis schedules were compared with respect to study duration and sample size, with impact of each rule (summarized as percent savings relative to no futility monitoring) on information, sample size, and calendar time scales over all trials. The average savings for each futility rule are shown in Table 1.

Results showed that testing alternative hypothesis and RCI rules yielded less savings comparing to other rules. The CP10% rule is similar to LIB20 rule with respect to trial duration for more than 3 interim analyses, but saved less on information and sample size scales. The CP 30% rule is too aggressive, stopping even when there is clinically meaningful treatment effect.

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A69
CALCULATING AND PRESENTING CONDITIONAL POWER AT INTERIM LOOKS FOR AN ADJUDICATED TIME-TO-EVENT OUTCOME
Susan Assmann, Eric Gerstenberger
New England Research Institutes Watertown, MA, USA

At an interim look for an ongoing clinical trial, the Data and Safety Monitoring Board may request conditional power calculations. In one approach, it is assumed that the event rates actually observed in each treatment group will carry forward for the remainder of the trial. Another approach assumes that, no matter what event rates have been observed to date, the event rates for the remainder of the trial will be a pre-specified set of event rates, e.g. those assumed when the study was designed.

Many clinical trials have outcomes which undergo adjudication, e.g. time to cardiovascular mortality or heart failure hospitalization for which an endpoint committee adjudicates the primary cause of death or hospitalization. At an interim look, some of the reported events may still be pending adjudication. Thus, the “observed rates” are not yet completely determined.

We will describe a simulation approach for calculating conditional power at interim looks with hypothetical examples. This method incorporates information from the “confirmation proportion” in each treatment group. It randomly chooses which subjects with pending status will be counted as having the event, and simulates time-to-event and time-to-loss for subjects who have not yet experienced the event or have not yet been enrolled. We report conditional power assuming that best-estimate current event rates in each treatment arm continue in the future. We also report conditional power based on pre-specified event rates, assuming Arm 1 is control treatment and assuming Arm 2 is control treatment. Thus, the conditional power report does not unmask which code refers to which treatment. This approach is used for TOPCAT, a multi-site trial of spironolactone for preserved ejection fraction heart failure, funded by NHLBI/NIH.
A70
ISSUES SURROUNDING INTERIM MONITORING OF A 3-ARMED CLINICAL TRIAL: EXPERIENCE FROM A STUDY OF OXYTOCIN REGIMENS FOR PREVENTION OF BLEEDING AFTER VAGINAL DELIVERY
Jeff M. Szychowski, Suzanne P. Cliver, Leslie A. McClure, John Owen, Alan T. N. Tita
University of Alabama at Birmingham, Birmingham, AL, USA

Planning and execution of interim monitoring procedures in 2-armed clinical trials are increasingly routine, yet are more multifaceted as the number of treatment arms increases. Complexities include identification of specific multiple comparisons of primary interest and establishment of interim monitoring stopping rules for superiority and futility. Other issues may arise including a lower than expected event rate. We present our experience with these methodological issues surrounding the planned interim analysis of a 3-armed clinical trial.

In the recent double-blind randomized trial, Oxytocin Regimens to Prevent Uterine Atony After Vaginal Delivery, 1798 women were randomized to receive 10U/500 ml, 40U/500 ml, or 80U/500 ml of oxytocin after delivery. The primary outcome was a composite of uterine atony, obstetric hemorrhage, and related medical, surgical or other treatment. The 10U vs 40U and 10U vs 80U comparisons were of primary interest. The study was powered to detect a rate decrease from 18% to 12% in either comparison. One interim analysis was scheduled after 2/3 of the women were enrolled, with early efficacy stopping boundaries approximated by the Lan-Demets spending function approximation to O'Brien-Fleming boundaries.

No safety issues were identified at the interim analysis and the Data and Safety Monitoring Board recommended continuation of the trial. Concern about the similar performance of two arms prompted a conditional power analysis for futility. Low conditional power to find a significant difference resulted in the discontinuation of the 40U arm. The study continued with the 10U and 80U arms with an increased sample size in response to a lower than expected overall event rate.

We present our experience to caution investigators about the issues encompassing interim monitoring in multi-armed clinical trials and to illustrate the importance of carefully identifying the primary hypotheses a priori and clearly defining strategies for interim monitoring and trial modification.

A71
EFFECT OF CELECOXIB ON ADENOMA COUNT IN A RANDOMIZED TRIAL OF CELECOXIB FOR THE PREVENTION OF SPORADIC COLORECTAL ADENOMA USING A ZERO-INFLATED POISSON (ZIP) MODEL WITH RANDOM EFFECTS
Meier Hsu, Ann G. Zauber, Mithat Gonen, Monica Bertagnolli
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Brigham & Women’s Hospital, Boston, MA, USA

Background: Celecoxib is an effective agent for the prevention of any adenoma recurrence in patients at high risk for colorectal cancer. A common approach for examining whether celecoxib reduces the number of adenomas has been to fit a Poisson regression model. However this method does not allow for data that exhibit a high proportion of zero events. This study describes an improved fit of observed adenoma counts using a ZIP model with random effects. Methods: Patients enrolled in the Adenoma Prevention with Celecoxib (APC) trial were randomly assigned to receive placebo (n=679), 200 mg (n=685) and 400 mg (n=671) of Celecoxib twice daily over three years. The number of adenomas removed was recorded at baseline and at follow-up colonoscopies performed at one and three years post-randomization. Data were fitted using Poisson and ZIP regression models, accounting for intra-subject correlation, respectively, with an exchangeable covariance and a covariance matrix assuming no correlation between the logistic and the Poisson random effects. Results: Treatment, baseline number of adenomas, and duration of follow-up are used in both the logistic and the Poisson submodels of ZIP (Table 1). Treatment with 200mg and 400mg both demonstrate a significant reduction in expected number of adenomas detected in a dose-dependent manner compared to placebo. The expected adenoma count is reduced after 3 years relative to 1 year and increased with more adenomas removed at baseline. Baseline adenoma count is also a significant factor in the odds of having zero recurrences, in excess of the Poisson expected zeros. ZIP predicted counts are more similar to the observed than Poisson (Table 2). Conclusion: Consistent with the analysis of any adenoma recurrence, treatment with celecoxib is effective in reducing the expected adenoma count. The ZIP model fits the data better than Poisson in describing the number of adenomas.


THE CHALLENGES OF FACILITATING AND SUPPORTING THE EFFICIENT AND SECURE EXCHANGE OF DATA IN A MULTI-SITE COOPERATIVE GROUP THAT IS FUNDED BY GOVERNMENT AND INDUSTRY

Scott Gould
Gynecologic Oncology Group Statistical & Data Center, Buffalo, NY, USA

The Gynecologic Oncology Group (GOG) Statistical and Data Center (SDC) is responsible for the collection and analysis of data obtained from GOG protocols. Since the GOG has members and industry partners that span the globe, there are many factors that govern the communication methods we use to securely exchange data. Federally funded groups, such as GOG, as well as private and public companies, must comply with the regulations of domestic, federal and state governments, as well as international organizations and foreign governments. In addition, each entity, including the GOG SDC, has its own internal policies stipulating how data must be secured for communication with outside entities. Many of these regulations and internal policies complement each other and help contribute to a layered model of security. Occasionally, policies of outside entities with whom we exchange data contradict our own internal policies or ideas of best practices. When such a conflict arises, it requires us to reevaluate how we secure our external data transfers. This continuous self-reflection on our secure communication policies has helped us and our partners enhance the secure exchange of data, while still facilitating information exchange in a manner that is manageable for all parties involved. We must also consider the steadily growing costs in terms of dollars and time for securing not just our own systems, but ensuring that our data is secure once it leaves the GOG. In addition to discussing the core components that make up the variety of secure networks utilized by the SDC, the presentation will outline challenges the SDC will face over the next few years and potential solutions.

LAPAROSCOPIC AND OPEN COLORECTAL CANCER SURGERY: AN OVERVIEW OF SYSTEMATIC REVIEWS

Guillaume Martel¹, Suleena Duhaime¹, Jeffrey S. Barkun², Robin P. Boushey¹, Craig R. Ramsay¹,³, Dean Fergusson¹

1Department of Surgery AND Ottawa Hospital Research Institute, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada; 2Department of Surgery, McGill University, Montreal, Quebec, Canada; 3Health Services Research Unit, University of Aberdeen, Aberdeen, UK

Objective. Several systematic reviews and meta-analyses populate the literature on laparoscopic surgery for colorectal cancer. The utility of this body of work is unclear. The objective of this study was to synthesize all such systematic reviews, to appraise their quality, and to determine whether areas of duplication exist across reviews.

Methods. A search for systematic reviews comparing laparoscopic and open surgery for colorectal cancer was conducted according to a comprehensive protocol (1991-2009). The primary outcome of interest was overall survival. The quality of included reviews was appraised using the AMSTAR instrument. Data abstraction and quality appraisal was carried out by two independent reviewers. Included reviews were synthesized, and outcomes of interests were compared across reviews. A citation analysis was carried out using simple matrices to assess the comprehensiveness of each review. Results. In total, 25 reviews were included (1994-2008). Twelve reviews included only randomized controlled trials. Rectal cancer was addressed exclusively by 4 reviews. Inclusion and exclusion criteria varied widely across reviews, as did the reported outcomes of interests. The median AMSTAR quality score was 6 (range 1-11). Previously published systematic reviews were poorly and highly selectively referenced. Previously published trials were not comprehensively identified and cited. Overall survival was evaluated by 5 reviews, none of which found a significant difference. Only two reviews provided a meta-analysis of time-to-event data. Among other outcomes, only operative time (longer for laparoscopy), length of stay in hospital (shorter for laparoscopy), and port-site metastases (no difference) yielded consistently congruent results across reviews. Conclusions. Existing systematic reviews of laparoscopic surgery for colorectal cancer are highly variable in methods and quality. A duplication of research efforts appears to exist in the literature. Survival outcomes are infrequently reported and their analysis appears superficial.
DIFFICULTIES IN RUNNING A RANDOMIZED CONTROLLED TRIAL IN THE REAL WORLD OF SOCIAL INTERVENTIONS IN DENMARK
Maiken Pontoppidan
SFI The Danish National Institute for Social Research, Copenhagen, Denmark

Although widely used in medical research in Denmark the use of RCTs in the social field is new and still sparse. SFI is currently running an RCT on two different therapeutic interventions for 150 families with children aged 5-12 displaying behavioral problems. Although the study has been carefully planned for many difficulties have arisen. According to Statistics Denmark the two interventions are widely used. In 2008 4000 families received practical home support and 9000 families received family therapy. However, after 1.5 year only 35 families have been included in the study in the seven participating municipalities. Directors of the municipalities support the study but caseworkers and therapists find it difficult to accept a randomized study. As caseworkers invite and enrol families into the study this is a problem. When studying implementation it became obvious that the two interventions were implemented very differently in the municipalities bringing more variation into the study. Effort was put into committing caseworkers to the study but the group has a high job turnaround and important knowledge is therefore lost. At an early point we found out that the two interventions were being mixed together and that families randomized to practical home support received family therapy. This was partly because therapists were being trained in family therapy and favoured this to practical home support. More strict definitions were created and the participating municipalities accepted to adhere to these. A recent problem encountered is that it is difficult to obtain assessments at 6 months. Obviously this is also a major problem that requires immediate attention if the study is to turn out successfully in the end.

HOW DID WE GET HERE FROM THERE? EXPERIENCES FROM N0147: A NORTH CENTRAL CANCER TREATMENT GROUP (NCCTG) PHASE III RANDOMIZED CLINICAL TRIAL
Michelle R. Mahoney, Daniel J. Sargent, Steven R. Alberts
Rochester, MN, USA; Rochester, MN, USA; Rochester, MN, USA

A phase III randomized clinical trial (RCT) often takes on a life of its own, becoming a dynamic process, especially during the enrollment and treatment phases. A common misconception among non-clinical trialists is that once a study has opened to enrollment, it then moves into “auto-pilot” for data collection, while the study team patiently waits for the required number of events (eg, recurrence, survival) to perform the planned interim and final analyses. Several factors impact the conduct of the trial during this time period that demand constant attention, monitoring, and decisions by the study team. For RCT N0147, this included unplanned enrollment interruptions, shortage of study agent(s), results of other phase III trials with similar agents/populations, emerging scientific knowledge, discovery of excessive toxicity in a subset of patients, as well as evolving database structures and changing data entry processes. For RCT N0147, these factors led to mid-stream study changes such as dropping treatment arm(s), providing short-term alternatives for agents, suspending enrollment, changing to centralized data entry (vs remote data capture), multiple updates to the Consent Form (and reconsenting patients), refining the patient population, adapting a new primary endpoint, as well as adding a pre-registration process for centralized testing of a biomarker shown to impact treatment outcomes (ie, KRAS). What started as 3 arm randomized trial, became a randomized 3x2 factorial study design (ie, 6 arms), finally changing to a straightforward randomized 2 arm trial with further mid-stream modifications requiring randomization based on a molecularly defined subgroup. Here, we will present the twists and turns of a NCCTG national 4,000 patient phase III colorectal RCT coordinated by the Mayo Clinic Comprehensive Cancer Center, providing examples of the impact of the issues and decisions addressed by the study team. Supported by NIH Grant CA25224.
A76
EXPLAINING TREATMENT-BY-SITE INTERACTION IN MULTISITE CLINICAL TRIALS: AN APPLICATION TO THE TORDIA CLINICAL TRIAL
Kaleab Abebe
University of Pittsburgh Pittsburgh, PA, USA

Currently, there is little discussion about methods to explain treatment-by-site interaction in multisite clinical trials, so investigators must explain these differences post-hoc with no statistical methodology in the literature. An example is the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study, which concluded that the combination of cognitive behavioral therapy and antidepressant medication (versus medication alone) had an effect on clinical response that was highly variable across sites. A secondary paper sought to explain these differences using a variety of univariate analyses, and came to the conclusion that differences in baseline clinical characteristics across sites were to blame. We used a mediated moderation framework (popular in the psychology literature) in a linear regression model with two treatments, two sites, and a single mediator variable. We then extended the treatment effect sizes proposed by the MacArthur Foundation Network group (Kraemer et al., 2001, 2002) to our model. Finally, the proposed methodology was illustrated on the TORDIA study, which showed that factors such as substance abuse and/or conflict behavior may help explain the treatment effect heterogeneity. The contribution of this is a framework for explaining treatment-by-site interaction in multisite clinical trials.

A77
CLINICAL TRIAL REGISTRIES - WHERE DO WE STAND?
Gabriele Dreier, Susanne Jena, Gerd Antes, Martin Schumacher
University Medical Center Freiburg

There are worldwide increasing efforts for implementing trial registries and databases, lead by governmental, industry, non-governmental and academic initiatives. Due to the increasing global activity in clinical studies, the implementation of registries should take place in a harmonized way. As a national clinical trials registry, as well as a member of the WHO International Clinical Trials Registry Platform (ICTRP) and the EudraCT Joint Operational Group (JOG), we can report from different perspectives. The talk will check the current situation and highlight the main topics to develop:
- The need for national registries in the light of opening the EudraCT database and 97,000 trials in ClinicalTrials.gov.
- How can patients be informed in their national language? Which tasks are to be performed from national registries?
- Ethics committees as the natural partner of clinical trials registries - is a working cooperation between ethics committees and clinical trials registries implemented? What should be done to improve cooperation?
- How can redundant work be avoided? How to facilitate sharing entered data?
- Where are we on the way towards harmonisation and standardisation of the data collection via global networks?
- Registry data as a indispensable source of information for researchers doing meta-analyses and HTA - Is it feasible, preferable and reasonable to expand clinical trials registries into results databases?

A78
DID THE EXTENSION OF CONSORT TO CLUSTER RANDOMIZED TRIALS RESULT IN IMPROVED QUALITY OF REPORTING AND STUDY METHODOLOGY?
Noah Ivers1, Monica Taljaard2, Jeremy Grimshaw2, Carol Bennett2, Stephanie Dixon3, Julia Taleban3, Andrew D. McRae4, Zoe Skea5, Robert Boruch6, Jamie Brehaut2, Martin P. Eccles7, Raphael Saginur2, Charles Weijer, Merrick Zwarenstein1, Allan Donner3
1Toronto, Ontario, Canada; 2Ottawa, Ontario, Canada; 3London, Ontario, Canada; 4Calgary, Alberta, Canada; 5Aberdeen, Scotland, UK; 6Philadelphia, PA, USA; 7Newcastle upon Tyne, UK

Background: Cluster Randomized Trials (CRTs) present investigators with unique methodological and analytical challenges which are often poorly described in the trial report. Suboptimal trial reporting can lead to questions regarding both internal and external validity and hinder the development of systematic reviews. In 2004, an extension of the CONSORT guidelines was published for CRTs. The impact of these guidelines on the reporting and methodological quality of CRTs is unknown.
Methods: We used an electronic search strategy implemented in Medline to identify reports of CRTs published in English language journals from 2000-2008, randomly sampling 300. Two reviewers independently abstracted 14 criteria related to quality of reporting and 4 other methodological criteria related to CRTs. We compared manuscripts published pre-CONSORT (2000-2004) to those published post-CONSORT (2005-2006 and 2007-2008) using Cochran-Armitage tests for trend.

Results: A significant improvement was found in four of fourteen reporting criteria: identification as cluster randomized; reporting whether outcome assessments were blind; reporting the number of clusters randomized; and reporting the number of clusters lost to follow up. No significant improvement was found in other criteria, including identification of the primary outcome, reporting of sample size calculation, and reporting of the intra-cluster correlation coefficient (ICC). Overall, there was minimal improvement in reporting with the manuscripts from 2000-2004 reporting a mean of 60% of criteria, those from 2005-2006 reporting 62%, and those from 2007-2008 reporting 67% (p=0.08). Additionally, there was no trend in the percent of trials that attempted to improve balance at baseline through restricted randomization or that accounted for the ICC in either the sample size calculation or the analysis.

Conclusion: The quality of reporting of CRTs has improved in some respects since the extension of CONSORT to CRTs was published, but further efforts are needed to ensure appropriate methodology is used and to improve trial reporting.

A79
THE INFLUENCE ON CONSORT ON THE QUALITY OF RCTS: AN UPDATED REVIEW
David Moher1, Lucy Turner1, Larissa Shamseer1, Amy Plint2, Laura Weeks1, Jodi Peters1, Doug Altman3
1OHRI, Ottawa, Canada; 2CHEO, Ottawa, Canada; 3Oxford

The Consolidated Standards of Reporting Trials (CONSORT) Statement was developed in response to concerns about the quality of reporting of randomized controlled trials (RCTs). It is an evidence-based minimum set of recommendations for reporting RCTs, intended to facilitate the complete and transparent reporting of RCTs and aid in their critical appraisal and interpretation. In 2006, Plint and colleagues published a systematic review examining the effectiveness of CONSORT for improving the reporting of RCTs in journals that have formally endorsed it (i.e. at minimum, recommend that authors use CONSORT). Despite poor methodology of some included studies, use of CONSORT was found to be associated with improvement in the quality of reporting of RCTs. Over five years have passed since Plint’s review and an update is needed. Objective: This systematic review will update Plint et al.’s systematic review. Details of which will be discussed during this presentation. Methods: Conventional systematic review methods employed in the original review by Plint et al. have been employed. The search for new studies spanned August 2005 – March 2010. Two independent reviewers screened studies for eligibility; extraction and validity assessment of studies were conducted by a single reviewer and a second reviewer performed verification. Results: In the 5 year period since publication of the original review by Plint et al., 42 new studies were identified which met eligibility criteria for this review. We will present preliminary findings during this session. Impact: This review will provide further evidence on whether CONSORT is effective at improving the reporting of RCTs. This information will be helpful to authors, peer-reviewers and journal editors in helping to decide whether to use CONSORT.
THE DURABILITY OF VACCINE EFFICACY ON THE INCIDENCE OF HERPES ZOSTER AFFORDED BY ZOSTAVAX

Xiaoming Li, Jane Zhang, Robert Betts, Vicki A. Morrison, Lawrence Gelb, Ruifeng Xu, Erik J. Dasbach, James, M. Pellissier, Gary Johnson, Ivan S.F. Chan

1Merck Research Laboratories, North Wales, PA, USA; 2CSPCC, VA Connecticut Healthcare System, West Haven, CT, USA; 3University of Rochester, Rochester, NY, USA; 4Minneapolis VAMC and University of Minnesota, Minneapolis, MN, USA; 5Washington University, St Louis, MO, USA

ZOSTAVAX has been approved in the US for the prevention of herpes zoster (HZ) in persons >=60 years of age based on the Shingles Prevention Study (SPS). A subset of SPS subjects was subsequently enrolled into an extension study (Short-Term Persistence Study, STPS) to collect longer-term vaccine efficacy (VE) data. To assess the long-term cost-effectiveness of ZOSTAVAX, the durability of VE was evaluated based on SPS/STPS. While it is important to consider durability of VE for all three study endpoints: HZ burden-of-illness (BOI), incidence of HZ, and incidence of postherpetic neuralgia (PHN), only durability of VE on incidence of HZ (VEHZ) is discussed here. VE measured by HZ BOI and PHN were both well- maintained in older subjects, while VEHZ declined with increasing age. This needs to be considered in cost-effectiveness analyses. To evaluate the durability of VEHZ, combined HZ incidence data from the SPS/STPS were parsed into bins defined by concurrent age and year from vaccination, so that the effects of age and time since vaccination on VEHZ could be evaluated. Poisson regression models were then used, with the number of HZ cases in each bin as the dependent variable, and concurrent age, year since vaccination, whether in the first year postvaccination, treatment, and interactions between treatment and each of the above variables as potential independent variables, and follow-up time as the off-set parameter. All models indicate a statistically significant age effect on VEHZ, but the effect of time since vaccination was not significant since most of the time effect occurred during the first year post vaccination. Hence, it is critical to consider the age effect on durability of VE on incidence of HZ (VEHZ) is discussed. The methodology for evaluating the durability of VEHZ will be discussed.

LEAN SIGMA IN THE NEW HEALTH LANDSCAPE: AN APPLICATION IN BIOSTATISTICS

Josephine Measures, Tim Strauss, Emma Bickford

Quintiles, KS, USA; Quintiles, NC, USA; Quintiles UK, UK

The pharmaceutical industry is facing unprecedented challenges from numerous sources including regulatory pressure to provide increasingly robust and detailed submissions along with pricing pressures to reduce the cost of health care globally. These challenges are passed onto CROs in the form of developing innovative approaches that reduce costs, increase quality whilst reducing time to market. As a result, CROs can no longer balance the cost, quality, time triangle in the traditional manner, focusing on one criterion at the expense of others.

A different approach based on lean sigma methodology tackles the cost, quality, time triangle in a systematic manner. It focuses on operational processes, as these of the core of what matters to CROs customers, and seeks to incrementally improve them to deliver value whilst fundamentally altering our ability to meet the challenges we face in the new health landscape.

This methodology has been applied within Biostatistics, starting with the development of the statistical analysis plan (SAP). The SAP is an important, and undervalued, document which governs the statistical analysis & presentation of safety and efficacy data. The aim of this project was to improve quality of the first draft SAP by identifying key drivers of quality. A cross functional team which included input from medics, project managers, data managers was formed to ensure that stakeholders were engaged in the improvement process and that as we move forward the SAP becomes a core document guiding decisions made by the broader project team.

Our solution is very detailed and includes small incremental changes in process but set within a framework of the changing industry landscape. This latter framework enables us to evaluate the process at a macro level to fundamentally change the role of a CRO statistician & SAP at these early stages to deliver increasing value to the customer.
NINDS committed $13 million to fund the CRC in May 2005 to evaluate the feasibility of engaging community neurologists in NINDS-sponsored research. The CRC created a web-based portal for physicians to learn about research and provided support to participate in NINDS-sponsored studies. 2,376 health care professionals registered including 1,279 physicians, 51 fellows/residents, 591 research coordinators, and 455 other health care professionals. CRC training programs were completed by 768 health care professionals. Certification to participate in research studies was initiated by 454 physicians; 117 of whom completed. CRC services included: an interactive web-based tool to check eligibility and locate sites for enrolling NINDS trials; a monthly lunch and learn series offering free CME (averaging 63 participants/session in final year); 5 research studies including a simple blood sample submission to a genetics repository, three on-going clinical trials, and one new clinical trial. 23 physicians contributed 1,801 blood samples over two years (29% African American; 49% Hispanic). A double blind, randomized clinical trial for chronic migraine treatment was designed with input from CRC physicians. Over two years, 65 sites screened 627 subjects and randomized 191. The percentage of the total screened and enrolled patients from 34 CRC sites participating in multiple CRC studies was 46% and 35%, respectively; 32% and 40% from other multi-neuro disease focused practices, and 20% and 25% from 12 headache centers. Only 12 CRC physicians contributed 40 subjects to one of three on-going studies, and no sites were certified for the other two. Barriers included compensation (20%) and activation requirements (75% increase in activation time).

Engaging community practitioners in clinical research activities within traditional research settings requires considerable support and special consideration toward site resources and expertise, and study design complexity. NINDS will pursue alternative mechanisms in the future to enhance community participation in research.

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### A83

**PREDICTORS OF ALL-CAUSES MORTALITY ON 6975 PATIENTS OF THE GISSI-HF TRIAL ON HEART FAILURE**

*Simona Barlera*, Luigi Tavazzi, Maria Grazia Franzosi, Roberto Marchioli, Elena Raimondi, Renato Urso, Donata Lucci, Aldo P Maggioni, Gianni Tognoni

1Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; 2Maria Cecilia Hospital, GVM Care and Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy; 3Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; 4Consorzio Mario Negri Sud, S Maria Imbaro, Italy; 5Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; 6Department of Neurological and Behavioral Sciences, Section of Pharmacology “Giorgio Segre”, University of Siena; 7ANMCO Research Centre, Florence, Italy; 8ANMCO Research Centre, Florence, Italy; 9Consorzio Mario Negri Sud, S Maria Imbaro, Italy

Background: Management of heart failure (HF) should be guided by an estimate of patient risk. Objective: To develop a prognostic model to assess the risk for medium term mortality for the Italian setting of HF treated patients in general clinical practice. Methods: We evaluated data from 6975 patients enrolled in the GISSI-HF trial with chronic HF and followed-up for 3.9 years (median). Multi-variable Cox regression models were developed using all the relevant baseline variables to predict all-cause mortality (n=1969 deaths). By means of a stepwise selection, the full final model included 24 predictor variables for all-cause mortality. A reduced model, considering only the most significant variables ranked according to the Wald Chi-Square (p < 0.0001) resulted to account for most of the prognostic information. This model was used to develop a nomogram of patient risk. The predictive accuracy of the two models was measured by the concordance probability estimate (CPE). Results: The discrimination ability of the reduced model constituted by 12 factors (CPE=0.693) was as good as the one obtained for the full final model (CPE= 0.70). Among the first 12 independent risk factors emerged in the reduced model, the three most powerful predictors were older age, lower left ventricular ejection fraction (beginning <40%), lower glomerular filtration rate (GFR) (beginning <60). Other independent predictors that increased
risk included chronic obstructive pulmonary disease (COPD), lower systolic blood pressure (up to 140), higher NYHA class, diabetes, male sex, higher uricemia (from 6.9 mg/dl), lower body mass index, lower hemoglobin and aortic stenosis. The reduced model was utilized to build a nomogram (see figure) to estimate the risk for death in individual patients. Conclusions: in a large contemporary CHF population, this model provides good ability to assess the risk for death confirming most of the risk factors emerged in recent trials.

A84
IMPUTATION OF SURVIVAL OUTCOMES IN CLINICAL TRIALS: RISK-STRATIFIED IMPUTATION IN INFORMATIVE CENSORING
George Howard\textsuperscript{1}, Richard E. Kennedy\textsuperscript{1}, Kofi P. Adragni\textsuperscript{1}, Hemant K. Tiwari\textsuperscript{1}, Jenifer H. Volks\textsuperscript{1}, Thomas G. Brott\textsuperscript{2}
\textsuperscript{1}Birmingham, AL, USA; \textsuperscript{2}Jacksonville, FL, USA

Differential withdrawal/dropout by treatment that can become informative censoring (risk of censoring is dependent on exposure variables) is a likely occurrence in many randomized trials due to changes in recruitment and eligibility criteria to minimize withdrawals. This type of censoring may lead to biased results favoring one treatment over another. Standard analytic approaches addressing missing data arising from censored patients may give unbiased estimates of treatment effects but underestimate the associated variance. In addition, current approaches to missing data that employ multiple imputation may not account for the effect of the covariate fail to remove this bias. We propose a new method, risk-stratified imputation, as an alternative to address informative censoring in the context of time-to-event analyses. Our simulations demonstrate that risk-stratified imputation gives unbiased estimates of treatment effect while maintaining appropriate coverage for the test statistic. A motivating example from a recent clinical trial is presented to demonstrate the utility of our method. The use of the risk-stratified imputation should facilitate the analysis of many clinical trials, in which one treatment group has informative censoring from a higher withdrawal rate that is related to treatment.

A85
ASCERTAINING DEMENTIA RELATED OUTCOMES FOR DECEASED OR PROXY-DEPENDENT PARTICIPANTS: AN OVERVIEW OF WHIMS SUPPLEMENTAL CASE ASCERTAINMENT PROTOCOL (SCAP)
Sarah A. Gaussion, Mark A. Espeland\textsuperscript{1}, John Absher\textsuperscript{2}, Barbara V. Howard\textsuperscript{3}, Beverley M. Jones\textsuperscript{4}, Stephen R. Rapp\textsuperscript{1}
\textsuperscript{1}Wake Forest University School of Medicine, Winston-Salem, NC, USA; \textsuperscript{2}Absher Neurology, Greenville, SC, USA; \textsuperscript{3}MedStar Research Institute, Hyattsville, MD, 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. Relying solely on clinic-based assessments of cognitive impairment may lead to biases in estimates of incidence and characterizations of risk factor relationships in older cohorts due to differential missing data.

The Women s Health Initiative Memory Study (WHIMS) enrolled 7,479 women, aged 65-79 years and free of dementia, in a clinical trial of postmenopausal hormone therapy who were followed for up to 13 years with annual two-staged clinic-based standardized protocols to identify incident probable dementia. A substudy of WHIMS, Supplemental Case Ascertainment Protocol (SCAP), a supplemental proxy-based protocol, involving telephone-administration of the Dementia Questionnaire, was designed to assess the cognitive status of women who could no longer attend clinic visits because they died (N=1058) or became dependent (N=228). Chi square tests were used to compare characteristics of women eligible for proxy-based versus clinic-based assessment. Risk factor relationships were described using proportional hazards regression.

Women who were eligible for proxy-based assessments tended to have worse cognitive impairment risk factor profiles and had higher rates of probable dementia (15.2% vs. 3.5%) than clinic-assessed participants. Augmenting the clinic-based cases with those identified from proxy interviews reduced undercounting and materially altered observed relationships that years since menopause, smoking status, diabetes and prior use of hormone therapy had with incident probable dementia.
Proxy-based assessments are necessary in longer-term studies to reduce ascertainment bias, undercounting of dementia cases and to characterize risk factor relationships. While potentially useful in reducing biases, these campaigns are unlikely to be adequate to eliminate biases fully.

A86

COMPARISON OF ADJUDICATED EVENTS TO INITIAL CLINIC EVENT REPORTING IN THE ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) TRIAL

Angela R. Kimel, Laura L. Lovato, Peter E. Linz, Jennifer Green, J. Thomas Bigger, Adrian Schnall, Loretta Sanders
Wake Forest University Health Sciences; Winston-Salem, NC, USA

The accurate and complete classification of outcome events is critical to the interpretation of clinical trial results. In an effort to ensure unbiased application of pre-specified event definitions the use of a blinded Clinical Endpoints Committee (CEC) has been a common practice in large multicenter clinical trials. In this design, clinical sites report an event and the CEC confirms that the event fulfills the pre-specified definitions. The use of a CEC is an expensive and time consuming process. Although felt to be necessary by many to reduce potential bias and increase accuracy of results, there is little literature comparing trial results using the official CEC adjudications versus the unadjudicated clinical site reports of events. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a study of 10,251 diabetic patients that used a composite primary endpoint of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction. This presentation reports the effects of centralized event adjudication on the total number of events counted in each component of the ACCORD primary outcome, and compares the overall ACCORD trial result by treatment arm using adjudicated trial results versus the unadjudicated results. Although there were a greater absolute number of events counted using the clinic report compared to the CEC classification (because adjudication removes events that do not fulfill the trial definition), the hazard ratios and their confidence intervals of treatment effects were virtually identical in the adjudicated and unadjudicated results.

A87

METHODS FOR CHOOSING A CUT POINT WHEN DICHOTOMIZING A CONTINUOUS RESPONSE A CASE STUDY OF PREDICTING INFANT SURVIVAL WITH HIGH RESOLUTION MELTING SCORE

Lei Wang1, Susan Eshleman2, Deborah Donnell1
1Fred Hutchinson Cancer Research Center, Seattle, WA, USA;
2Johns Hopkins University School of Medicine, Baltimore, MD, USA

Often when analyzing data from clinical trial or epidemiology study, we dichotomize a continuous exposure variable and report a measure of association, such as odds ratio or hazard ratio, between the dichotomized variable and an outcome such as disease or death. Questions arise as to how the cut point for dichotomization is chosen, especially when a theory-based threshold does not exist. A high resolution melting (HRM) assay was developed to measure HIV diversity without sequencing. In one analysis, we used the HRM score to evaluate the relationship between HIV diversity and survival in Ugandan infants using data from HIVNET 012, a phase IIB clinical trial to evaluate the efficacy of oral Nevirapine and the efficacy of oral AZT in infants born to HIV-infected mothers for prevention of vertical HIV transmission. Predictive strength of various cut points was first evaluated using receiver operator characteristics (ROC). Plotting hazard ratio (HR) estimate and confidence intervals over a range of cut points may offer more information about trends in the association of interest as the cut point changes.
TIME TO COMPOSITE OUTCOMES WITH SEMI-COMPETING RISK: A COMPARISON OF METHODS TO DETECT TREATMENT HETEROGENEITY WITHIN A COMPOSITE OUTCOME
Janice Pogue, Lehana Thabane, Changchun Xie, PJ Devereaux, Salim Yusuf
McMaster University, Hamilton, Ontario, Canada

Introduction: Lim (2008) found that among cardiovascular trials that use a composite outcome, 98% include death in these composite outcomes. Mortality is frequently less sensitive to treatment compared to non-fatal outcomes (Montori, 2005) and it censors the observation of all non-fatal outcomes included in the composite. We can examine treatment heterogeneity within this type of composite outcome using time-to-event analysis. The power, bias, and precision to detect treatment heterogeneity among the components of a composite outcome are contrasted for three different time-to-event models (unadjusted Cox regression, marginal models, and frailty models) while varying the treatment effect for the fatal outcome within the composite. Methods: Simulations were completed for a two-group, 5,000 participant, time to event trial using a composite outcome containing both a fatal and non-fatal outcomes. Data were simulated using a gamma frailty model, where the treatment effect of the non-fatal outcomes remained constant, while the treatment effect of the fatal outcome was varied. Three models were fitted: unadjusted Cox regression, marginal, and frailty models. For each model, a treatment heterogeneity test was conducted between the two outcomes. Results: Marginal and frailty models have similar power to detect treatment heterogeneity as the treatment effect on a fatal outcome varies. Both unadjusted Cox regression and marginal models showed a systematic underestimate of the interaction coefficient for treatment differences by outcome type (fatal/non-fatal), but the marginal models had the smallest standard errors for the interaction coefficient. Conclusions: Our results suggest that both the marginal and frailty models are appropriate choices for estimating treatment heterogeneity for analysis of time to composite outcome composed of fatal and non-fatal components.

ESTIMATION OF SURVIVAL FOR ALL TREATED PATIENTS IN THE RANDOMIZED DISCONTINUATION TRIAL DESIGN
Theodore Karrison, Gary Rosner, Walter M. Stadler, Mark Ratain
University of Chicago, Chicago, IL, USA

The randomized discontinuation trial (RDT) design (Rosner et al., 2002) is an enrichment design that has been used in phase II oncology trials to evaluate the effects of cytostatic agents. In the RDT design all patients receive treatment during an initial, open label run-in period of duration Patients with objective (partial or complete) response remain on therapy while those with early progressive disease are removed from the trial. Patients with stable disease are randomized to either continue active treatment or be switched to placebo. The main analysis compares subsequent outcomes, for example, progression-free survival (PFS), between the two randomized arms. This design was used to evaluate the disease-stabilizing activity of sorafenib in patients with metastatic renal cell cancer (Ratain et al., 2006). The median PFS following randomization in the sorafenib group was found to be 24 weeks compared to 6 weeks in the placebo arm (p=0.0087).

As a secondary objective, Ratain et al. estimated PFS for all sorafenib treated patients, measured from the time of entry into the study, by combining information from the run-in and post run-in periods. For PFS is estimated by the observed proportion of patients progression-free at time among all patients enrolled. For this estimate can be expressed as where is the estimated probability of response during the run-in period, is the estimated probability of stable disease, and are the Kaplan-Meier estimates of PFS in the responders and patients with stable disease randomized to treatment, respectively. In this presentation we derive an estimate of the variance of enabling the construction of confidence intervals for both and the median. Simulation results indicate that the method provides accurate coverage rates.
A90
APPLICATION OF EXCESS ZERO METHODOLOGY TO ORAL HEALTH-RELATED QUALITY OF LIFE: PEARL NETWORK FINDINGS
Abigail Matthews, Don Vena
EMMES Corporation, Rockville, MD, USA

Oral health research has recently focused on evaluating quality of life (QoL), with the most common tool being the Oral Health Impact Profile (OHIP). The score for the 14-item version of the OHIP survey is the total number of impacts reported (0-56), but is not particularly sensitive to small changes in QoL, which results in many study participants reporting zero impact. One dental practice-based research network, Practitioners Engaged in Applied Research and Learning (PEARL), utilized the OHIP-14 in four of its studies. All 4706 scores were highly overdispersed using multiple tests, including the Fisher overdispersion test. Over 65% of subjects reported 0 impacts, and the distribution of scores has been shown to differ significantly across protocols. Exploration of poisson, negative binomial, zero-inflated poisson (ZIP) and zero-inflated negative binomial (ZINB) models indicated the best fit of the data was the ZINB using AIC. However, in this model the dispersion is highly significant, indicating that there is residual overdispersion. For each of the models, protocol was highly significant (all p<0.001), as anticipated. An alternative approach (Lachenbruch, 2001) is to consider a two-part composite statistic: a test of the difference in the proportion of subjects reporting zero impacts across protocols, and a test of the difference in the magnitude of reported non-zero scores across protocols. For the first component, we utilize the 3df chi-square test of association from the corresponding 2x4 contingency table. The second component utilizes the 3df chi-square global test of association assuming a negative binomial model, which indicated no overdispersion (Pearson's chi-square/DF<2). As expected, the 6df composite chi-square test was highly significant (p<0.001). These results are particularly interesting in that once the zero impacts are excluded, the data fit a NB model indicating the overdispersion of the total score was likely due to excess zero counts and not heterogeneity.

A91
THE IMPACT OF ASSOCIATION BETWEEN ENDPOINTS ON PERFORMANCE IN SEAMLESS PHASE II/III CLINICAL TRIAL DESIGNS
Meihua Wang1, James J. Dignam1,2
1Department of statistics, Radiation Therapy Oncology Group, American College of Radiology, Philadelphia, PA, USA; 2Department of Health Studies, University of Chicago, Chicago, IL, USA

The phase II/III seamless design aims to add logistical efficiency and maximize the contribution of patient information. We examine the impact of correlation between endpoints for the two trial stages on type I error, power, study duration and expected sample size.

We consider the endpoints of progression-free survival (PFS) for phase II and overall survival (OS) for phase III, simulated from a bivariate exponential distribution. We evaluate the impact of correlation under a) no treatment effect on either PFS or OS (global null); b) treatment effect on both PFS and OS (global alternative); c) treatment effect on PFS, but not on OS (PFS only alternative) and d) treatment effect on OS, but not on PFS (OS only alternative).

The simulation results demonstrate: 1) under the global null, strong correlation leads to slightly lower probability of going to the phase III and lower probability of false positive conclusions in phase III, compared to moderate and weak correlations; 2) under the global alternative, strong correlation leads to higher probability of going to phase III and higher probability of positive phase III claims; 3) there is little influence on study duration and expected sample size with varying correlations under either global hypothesis; 4) under the PFS only alternative, strong correlation leads to higher probability of going to the phase III and higher probability of false positive phase III conclusions, longer study duration and larger expected sample size; 5) under the OS only alternative, strong correlation leads to lower probability of going to the phase III and lower probability of positive phase III claims, shorter study duration, and smaller expected sample size.

We conclude that under either global hypothesis, the presence of strong correlation is a desirable feature with respect to the type I error and power for this design.
A92
ROBUST INFERENCE VIA PERMUTATION DISTRIBUTIONS
Jitendra Ganju, Xinxin Yu, Julie Ma
Amgen, Inc., University of Wisconsin, Amgen, Inc.
Pre-specifying one method of analysis for clinical trial data is challenging because the model may prove to be inadequate once the data become available. Models are wrong for many reasons, including omitting necessary covariates, incorrect transformations, or violations of important assumptions. Is there a way to minimize the risk? The talk will describe a method for robust inference in clinical trials that is much more reliable than the conventional approach of pre-specifying a single method of analysis.

A93
ANALYSIS OF INCOMPLETE NON-NORMAL LONGITUDINAL LIPID DATA
Jiajun Liu, Devan V. Mehrotra, Xiaoming Li
Merck Research Lab, Upper Gwyneda, PA, USA
It is well recognized that certain lipid endpoints (e.g., triglycerides) are not normally distributed, and missing data due to dropouts in lipid trials are common. A popular analytic approach is to use last observation carried forward (LOCF) to tackle missing data, followed by a Wilcoxon rank sum test to compare treatment groups. Point and interval estimates of the treatment effect can be obtained via inversion of the rank-based test. This approach might appear to have reasonable type I error properties, but the corresponding estimation bias and spurious impact on power due to the LOCF component can be problematic. We propose an alternative method that replaces the LOCF component with multiple imputation, while retaining the subsequent robust regression analysis component. Simulation results and a real example are used to illustrate the benefits of our proposed approach.

A94
REGRESSION WITH LATENT VARIABLES: A BETTER WAY TO ANALYZE COMPOSITE SCORES FROM INSTRUMENTS FOR SUBJECTIVE OUTCOMES IN CLINICAL TRIALS
Chengwu Yang, Anbesaw Selassie, Barbara Tilley, Ruth Greene
College of Medicine, Pennsylvania State University, Hershey, PA, USA
Regression with latent variables: a better way to analyze composite scores from instruments for subjective outcomes in clinical trials Chengwu Yang, Anbesaw Selassie, Barbara Tilley, Ruth Greene College of Medicine, Pennsylvania State University, Hershey, PA Subjective outcomes such as depression are prolifically used in clinical trials, and they are usually measured by composite scores from instruments such as the Center for Epidemiologic Studies Depression Scale (CES-D). While target populations are commonly heterogeneous, most instruments were developed using homogenous samples and hence a big concern of validity. One of the most critical validity issues is whether the proposed factor structure of the instrument, i.e., which specific items in the instrument can be summarized into a specific composite score, is sustained in the patients recruited. Although predominately used in practice when analyzing composite scores from instruments in trials, the conventional multivariate regression that directly regresses these scores on covariates (e.g., treatment) cannot investigate if the instrument holds the proposed factor structure and therefore false results may occur. However, regression with latent variables, e.g., the multiple-indicator multiple-causes (MIMIC) model, that regress the latent domain scores on covariates has the following important and appealing advantages: 1). it can assess factor structure of an instrument; 2). it can investigate if any covariate effect on the composite scores is contaminated by measurement bias, i.e., differential item functioning (DIF). Three situations exist when applying MIMIC models to composite scores: 1). the instrument’s factor structure is sustained, and there is no DIF; 2). the instrument’s factor structure is sustained, but there is DIF; 3). the instrument’s factor structure is not sustained. Three datasets from trials and medical research projects that corresponding to each of these three situations are analyzed using both of the two methods, and results are compared. Recommendations for analytic strategy under different situations are made.
A95

ADAPTIVE DESIGN FOR CLINICAL TRIALS: PERSPECTIVES FROM A WORKSHOP
Christopher S. Coffey1, Bruce Levin2, Christina Clark3, Cate Timmerman4, Janet Wittes5, Peter Gilbert6, Sara Harris4

1Department of Biostatistics, University of Iowa, Iowa City, IA, USA; 2Department of Biostatistics, Columbia University, New York, NY, USA; 3Foundation for Interdisciplinary Motor Neuron Medicine, Metamora, MI, USA; 4Palladian Partners, Inc., Silver Spring, MD, USA; 5Statistics Collaborative, Inc., Washington, DC, USA; 6National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

The biomedical research community constantly seeks dependable and reliable ways to improve clinical research. This has led to considerable interest in adaptive clinical trial designs, which provide the flexibility to make adjustments to aspects of the design of the trial based on data reviewed at interim stages. Adaptive designs, while useful in many situations, can be particularly helpful in trials examining therapies for rare or rapidly deteriorating diseases. Statisticians and clinical investigators have proposed or implemented a wide variety of adaptations in clinical trials, but specific approaches have met with differing levels of support. Within industry, investigators are actively exploring the benefits and pitfalls associated with adaptive designs. For example, a Pharmaceutical Research and Manufacturers of America (PhRMA) working group on adaptive designs has engaged regulatory agencies in discussions about adaptive designs. Many researchers working on publicly funded clinical trials, however, are not yet fully engaged in this discussion.

We organized the Scientific Advances in Adaptive Clinical Trial Designs Workshop to begin a conversation about using adaptive designs in publicly funded research. Held in November of 2009, the 1½-day Workshop brought together representatives from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the European Medicines Agency (EMA), the pharmaceutical industry, non-profit foundations, the patient advocacy community, and academia. The Workshop offered a forum for participants to address issues of adaptive designs that arise at the planning, design, and execution stages of clinical trials, and to hear the perspectives of influential members of the clinical trial community. The participants also set forth recommendations for guiding action to promote appropriate use of adaptive designs. This presentation will summarize the key recommendations that were produced as a result of this workshop.

A96

A BIOMARKER-BASED ADAPTIVE TWO-STAGE RANDOMIZED PHASE II STUDY DESIGN
Virginia L. Filiaci, Mark F. Brady

Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, USA

The use of biomarkers in phase II studies is typically restricted to screening for eligibility, use as a surrogate endpoint or exploratory assessment of its relationship with the study endpoint. In early drug development, often there is insufficient clinical evidence to justify the evaluation of a new drug only in a subset of patients defined by a purported predictive biomarker. Additionally, the expected frequency of the outcome among the biomarker-defined populations may not be available from historical studies. An alternative design strategy that incorporates randomization with a reference arm and interim analysis of a biomarker-treatment interaction to screen regimens for activity is proposed. This design uses a preliminary relative assessment of a qualitative difference in treatment benefit between the two cohorts defined by a biomarker. The biomarker-defined cohorts (e.g. negative and positive) can be assessed separately to estimate the probability of response. The sample size can be determined strictly on the basis of achieving desired operating characteristics in the population thought most likely to benefit. This design incorporates the biomarker into the trial for hypothesis testing, permits an evaluation across subgroups and for a correlation with the endpoint, provides some protection against a faulty biomarker, can allow for assessment of other biomarkers and most importantly allows for an informed phase III design. The design is not recommended when the biomarker subgroup that is thought to benefit is small relative to their complement. Operating characteristics of this design will be compared with other trial designs from the literature.
Relapsed acute lymphoblastic leukemia (ALL) remains a significant clinical challenge. The Children’s Oncology Group (COG) evaluates new agents in relapsed ALL in combination with a standard reinduction platform. This single arm phase II approach relies on historical controls, requiring a new trial for each new agent. A novel trial design was developed to facilitate evaluation of multiple agents in combination with a standard platform. In this setting, the sequential randomized phase II screening design is proposed to permit evaluation of several new agents on a common platform in a single trial. Patients are randomized between control and experimental arm. As new agents are tested sequentially, the randomization ratio changes with each new agent. Let T1, T2 and T3 be 3 experimental arms, each compared to control arm C as a sequential 2- arm randomization. Patients are randomized 1:1 between C and T1; T1 is picked if its second remission (CR2) rate is better than C. Patients are then randomized 1:2 between C and T2. CR2 rates for controls in the two randomizations are compared at the 5% significance level. If not different they are pooled to be the controls to be compared to T2; otherwise, only current controls are used to compare with T2. Patients are then randomized 1:3 to C and T3; the previous controls are pooled with C to compare CR2 rates with T3. However, if CR2 rates in the first two controls are different these historical controls are not pooled with C, and patients are randomized 1:1 to C and T3. It is clear that the sequential randomization ratios can reduce total sample sizes and shorten trial length. It is also helpful in maximizing accrual to trials for rare diseases, where there is not sufficient motivation for participating sites to get regulatory approvals and open the trial locally.

Results of medical tests such as those used for screening or diagnostics are often linked to a clinical treatment decision. For instance, a positive test would lead to treatment A while a negative test would lead to treatment B. With the blossoming use of biomarkers, genetics, imaging and computational modeling to identify current or future disease, these medical tests should not only be judged for diagnostic accuracy but also for clinical value. However especially for medical tests that identify a low percentage of positive cases, traditional randomized control trials can be large and expensive.

Bossuyt et. al. (2000) proposed a more efficient trial design where subjects were tested with both the new and established medical test. Only those with discordant tests were randomized to treatment A or B. Analysis of study results was described nonspecifically in the aforementioned paper. Here we explore the ability to analyze differences in treatments, test results and test methods. In addition we quantitatively examine the efficiency gain based on sample size.

With the appropriate analysis for the clinical question, we also extend Bossuyt’s design to accommodate serial medical tests. These cases can arise in cancer prevention screening which may be done biannually over a ten year period or in medical tests used in recurrent diseases. In these cases, subjects with discordant tests are randomized to either treatment. For future tests, subjects must remain on the same medical test, which is known from the first treatment randomization assignment. If the disease and intervention permits, crossover medical testing trials can also be performed.

More efficient and feasible randomized trials that study clinical value for paired medical tests should be developed in light of the increased modalities used for disease prediction which determine treatment decisions.
Many elements contribute to phase II trial design, including randomisation, endpoint selection, and statistical design. While literature exists that discusses each of these elements individually, we are unaware of any resource that brings all elements together. We have developed a guidance manual for the design of phase II trials in cancer, highlighting key points for consideration, and offering a structured and systematic approach to trial design. Results of a systematic literature review of phase II trial design methodology applicable to cancer trials (previously reported at SCT) were used to form the basis of the manual. Key elements of trial design included are: clinical considerations; trial aim; outcome of interest; outcome measure distribution; randomisation; design category; and practical considerations. The manual is focused to the cancer setting, however is transferable to other disease areas. It centres around a flow diagram that guides the reader through specific elements of phase II design. Following this, the points are discussed in detail, providing selection criteria for each. Phase II design methodologies identified from the literature review form a library of over 100 available statistical designs, providing a wealth of information to researchers. Each individual design is briefly summarized, including details of programming requirements and early trial termination options. The manual incorporates key points for consideration in the design of phase II trials in cancer, providing a structured and systematic approach to trial design, encouraging interaction between the clinician and statistician. With the aid of key selection criteria researchers may identify phase II designs appropriate to their specific criteria, and may incorporate additional elements such as programming to aid decision making. This provides a valuable tool to researchers in designing high quality phase II trials.

In many cases there is a need to compare novel treatments to active treatments where interest focuses on non-inferiority (NI), instead of superiority of the novel treatment. The study design can strictly focus on the NI hypothesis of efficacy or safety with the assumption of no other differences between the two treatments of interest; or it can focus on the NI of efficacy with a gain (superiority) in other treatment characteristics. The literature on the design, conduct and analysis of NI trials is continuously evolving. Several design issues continue to be debated including assay sensitivity, choice of NI margin and optimal analytic approaches. Although there is a good amount of literature on the characteristics of NI trials and several methodology papers as well as the recent FDA draft guidance, to date, there has been relatively little in the literature documenting actual experiences with implementing the available statistical methodology for NI trials. This presentation serves as a case study and highlights some of the challenges encountered in the design of a Phase III NI trial in status epilepticus that is being conducted by the Neurological Emergencies Treatment Trial Network (NINDS, U01 NS059041) under an FDA Investigational New Drug application. The authors highlight their interactions with the FDA and their application of available methods and approaches to address the conduct of an NI trial rather than a superiority trial, choice of the active control and NI margin, and incorporation of interim analyses for efficacy and futility.
ESTIMATING CLINIC STAFF TIME FOR PATIENT VISITS IN THE ACCORD TRIAL

Laney S. Light, Mohammed K. Ali, Lawrence J. Fine, Alice C. Leone, K.M. Venkat Narayan, Patrick O’Connor, Adrian Schnall, Debra L. Simmons, Abraham Thomas, Ping Zhang, Wenke Hwang

Wake Forest University School of Medicine, Winston-Salem, NC, USA

Estimating costs associated with clinical interventions is an essential, but still evolving component of economic evaluations alongside clinical trials. We describe methods used to assess clinic staff time, a major component of the intervention cost, to deliver a multi-faceted intervention in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and preliminary results. ACCORD is a U.S. and Canadian multicenter randomized trial designed to test the effects of intensive versus standard medical strategies of glycemia, blood pressure and lipid control for reducing cardiovascular events in 10,251 participants with type 2 diabetes. Estimation of time clinic staff spent delivering interventions was done in 75 of 77 sites from the seven clinical coordinating centers (CCN). Representatives from the CCNs trained their clinic staff on completing the survey. Staff estimated time spent and percent of visits attended by 13 pre-defined personnel roles for scheduled and unscheduled phone and in-person visits. Separate estimates were obtained for participants in each study arm and for the first year of the study versus the second year onward. Tools included guidance on time estimation for including intervention activities and excluding research ones. Median total time spent on clinic visits ranged from 17 minutes for unscheduled phone calls to 93 minutes for scheduled clinic visits and varied across clinics (interquartile range=10 to 28 and 62 to 120, respectively). Median total time for scheduled clinic visits ranged from 84 to 98 minutes by study arm. Scheduled clinic visits in the first year took longer than visits in the second year onward (median=101 vs. 85 minutes). Registered nurses contributed the largest amount of time to patient visits, followed by nurse practitioners. Results from this survey will be combined with visit frequency to calculate personnel cost of the interventions.

EVALUATION OF IMBALANCE IN STRATIFIED BLOCKED RANDOMIZATION

BY INVESTIGATING VALIDITY OF HALLSTROM & DAVIES MODELS

Guenther Kundt, Aenne Glass

Institute of Biostatistics and Informatics in Medicine and Ageing Research, University of Rostock (Germany)

Objectives: If in a clinical trial prognostic factors are known in advance, it is often recommended that randomization of patients should be stratified. The best-known method is permuted-block randomization within strata. But it suffers from the disadvantage that imbalance still occurs in the trial as a whole if there are a large number of strata, or/and the block sizes are too large. Results of Hallstrom and Davies [1] are appropriate to evaluate the risk of such a troubled situation by using two special cases of their general variance formula: assuming either a binomial or uniform distribution model. As it is merely generally argued for whichever practical situations these cases are valid, additional refined investigations are required to reveal conditions for correct application.

Methods: We investigate the range of validity by performing computer simulations varying a number of trial characteristics, and discuss application of results for practical situations. Results: Depending on block size, binomial distribution model is valid for a permitted average maximum number of patients per stratum between 14% and 57% of block size, whereas the uniform distribution model works adequately for 65% to 77%. In an intermediate range of invalidity of both special cases, implementation of a simulation study is necessary to compute the probability distribution of absolute differences. Conclusions: Our results are important if choosing the permuted-block randomization within strata. We make a contribution to using this method more accurately in future with a lower risk for an intolerable overall imbalance.


MONITORING THERAPY SESSIONS FOR ADHERENCE TO PROTOCOL

Heather Eng, Theresa Sax

University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA

The TRIAD Study (Treatment of Insomnia and Depression) is a multicenter randomized clinical trial to determine whether the combined intervention of standard pharmacotherapy (P) for depression plus cognitive behavioral
therapy for insomnia (CBTI) improves the outcomes of patients with major depressive disorder and insomnia, as opposed to a combined intervention of pharmacotherapy with a placebo desensitization therapy (DTI).

In order to confirm study therapists adherence to protocol guidelines, all sessions are audio recorded, and on a quarterly basis, a random 10% sample of each type of session (P, CBTI, DTI) is selected for review by independent monitors.

A system has been developed to enable the monitors to efficiently review and rate the selected sessions. Upon logging into the system, the monitor is presented with a list of sessions to be reviewed. The monitor clicks on a session for review and is presented with a data collection screen to record adherence and rating scales appropriate for the type of therapy being reviewed. At the top of the screen is a control that allows the monitor to play the session recording. The control also includes buttons to pause, reverse, and fast-forward the recording, allowing the monitor to carefully review the session and thus more effectively rate the therapist.

Data entered on the adherence and rating scales are stored directly in the project database, from which the data coordinating center can report and review adherence scores. Therapists who demonstrate a deviation from the protocol are provided with feedback, and frequent or major deviations require retraining and recertification before the therapist can continue in the study.

The system is designed to handle both audio and video recordings and can be readily implemented in other research studies.

**P04**

**PROGRAM IN R TO CALCULATE ADHERENCE WITH MEDICATION REGIMEN**

Robert G. Edson  
VA Cooperative Studies Program Coordinating Center Palo Alto, CA, USA

R is a language and environment for statistical computing and graphics comparable to the S language and environment available as free software under the terms of the Free Software Foundation’s GNU General Public License in source code form. Given a file with dispense and return dates and a count of unused pills for each drug card and a file with dates of visits and other significant events for each subject (e.g., date subject permanently taken off medication), for any study period this program uses basic R functions to determine for each subject if adherence can be calculated (i.e., when each drug card dispensed during that period was returned by the end of the period and had a count of used pills) and if so to compute adherence. The program accounts for days when the subject was temporarily off drug based on dispense and return dates. Adherence results can easily be summarized by various factors, such as by level of adherence within treatment group. Another component of the program determines for each time period between study visits whether the subject met the adherence criteria (e.g., between 80% and 110% of the prescribed number of pills were taken) and then calculates the percent of time periods for which the subject was adherent. The output from R can be stored as a text file and then read into a spreadsheet software package to put the table into the desired final format for inclusion in a report.

**P05**

**A COMPLEX WEB-BASED STRUCTURE FOR COORDINATING REVIEW AND TRACKING PROGRESS OF ANCILLARY STUDIES IN THE NATIONAL LUNG SCREENING TRIAL**

Jennifer Rosenbaum, Brenda Brewer, Janet Lawler-Heavner, Kathy Clingan, Miriam Galbraith, Sekou Yoda  
Westat, Rockville, MD, USA

The 33-site National Lung Screening Trial (NLST) is comprised of the National Cancer Institute contract-funded Lung Screening Study (LSS) and a component funded by an NCI grant to the American College of Radiology Imaging Network (ACRIN). The NLST Executive Committee mandated three separate review procedures for ancillary studies that use data solely from the ACRIN component, those that use data solely from the LSS component, or those that use data from the combined NLST.

Coordinating and tracking the complex review process of ancillary research for this two-component trial from concept through publication required a robust yet flexible system, accessible to multiple users in various roles. The Study Tracking and Review System (STARS) is a Web-based tool developed by the NLST/LSS Coordinating Center (CC) to support the review of ancillary research for multiple projects. STARS was tailored to meet the
unique needs of the NLST, enabling automated tracking of multi-step review processes for NLST/LSS and combined NLST ancillary research.

NLST STARS eliminates manual tracking, allowing intervention by the CC Publications Coordinator when necessary. This tool facilitates communication with investigators and reviewers through e-mail notification at each step in the review process. After approval, NLST STARS automatically monitors study progress through status updates.

Frequent challenges to the development and implementation of NLST STARS were encountered as needs of the trial emerged and changed. The presentation will describe these challenges, provide an overview of our streamlined process for monitoring ancillary studies and their resulting publications and presentations, and describe our approach to enhancing STARS in response to evolving policies and user feedback.

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**P06**

**MONITORING THE PROGRESS OF CLINICAL TRIALS IN A NETWORK SETTING: EXPERIENCE FROM THE NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK**

Paul VanVeldhuisen, Colleen Allen, Aimee Wahle, Li Lu, Carol Cushing, Paul Wakim, Betty Tai

*NIDA Data and Statistics Center 2, The EMMES Corporation, Rockville, MD, USA; NIDA Center for the Clinical Trials Network, Bethesda, MD, USA*

The National Drug Abuse Treatment Clinical Trials Network (CTN), established by the National Institute on Drug Abuse (NIDA), has developed a comprehensive set of web-based standardized Trial Progress Reports (TPR) to use as a management tool to effectively monitor the progress of on-going clinical trials in real-time. These reports track the progress of each trial within the CTN from the date of first randomization to final closeout and publication of main results. The content includes areas from all aspects of the clinical trials: recruitment, retention, quality assurance, and regulatory. Many of the reports in the TPR are updated daily and all reports are web-based and are available on a secure website to provide real-time access to critical trial information.

The TPR provides both a big-picture view of the NIDA CTN trials and a very detailed view to meet the needs of the varied audience, which include: (1) the sponsor and study leadership to assess the overall progress of multiple on-going studies; (2) the protocol lead teams to monitor their respective studies in order to identify areas of concern on an individual site level; and (3) the investigators and staff at each participating site within a protocol to monitor their individual site’s performance against other sites.

Metrics have been developed for key study components to provide feedback at a glance on the progress of the trials. These metrics have been assigned color-codes, where green denotes good performance, yellow where problem areas are identified, and red where poor performance is noted and remedial actions required.

The TPR has allowed the NIDA CTN leadership and protocol teams to monitor and intervene in the critical aspects of recruitment, retention, data quality, and treatment implementation to improve upon the overall quality of the research being conducted.

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**P07**

**EXPERIENCES OF DELIVERING A PRACTICE-BASED RANDOMIZED CONTROLLED TRIAL**

Presenting Author: Clare Jones

Co-authors: Keith Milsom, Martin Tickle

*The University of Manchester, Manchester, UK*

In the UK, most dental treatment is provided in ‘family’ primary care general dental practices. The majority of dental research, however, is carried out in academic or specialist care institutions, often including participants with different demographics and oral health to the family dental practice population. Whilst there is a need to deliver practice-based research, a number of barriers prevent dentists from engaging in this activity. This is reflected in the fact that there are relatively few practice-based randomized controlled trials investing clinical interventions reported in the dental literature.

A randomized controlled trial (RCT) based in three ‘family’ dental practices investigated the outcomes of single-visit scale and polish, when this is provided at different frequencies. This clinical trial involved 369 participants followed up over a two-year period. The project involved collaboration between university academics and primary
care ‘family’ dental practitioners. In addition to testing the research hypotheses, the trial provided an opportunity to gain ‘hands-on’ experience of delivering practice-based research, overcome the associated obstacles, and inform future practice-based projects, based on first hand ‘trial and error’. The study highlighted differences in the behaviors, beliefs and practices of academic researchers and clinical dentists. The main issues that arose and the way in which these were managed are presented. Most related to:

Research literacy – including understanding the timescales, scope and limitations of the trial.

Financial implications – including impact of research upon routine (contracted) service provision

Practicalities of running a practice-based trial – including physical space requirements, recruitment and retention of participants, administrative support.

Practice-based clinical trials investigating common and costly treatments are necessary to obtain high quality evidence with which to inform the decisions of dental commissioners, clinicians and patients. This can ensure that publically-funded dental services utilize resources appropriately, and that effective care is provided for those accessing both state-funded and private services.

**P08**

**CHALLENGES AND LESSONS LEARNED IN A CLUSTER RANDOMIZED TRIAL IN THE COMMUNITY**

Martina Mueller, Elaine Amella, Angela Fraser

*Medical University of South Carolina, Charleston, SC, USA*

A USDA-funded trial was designed to test the effect of a newly created nutrition/food safety curriculum using the existing federally- and state-funded congregate meals program to reach older adults. The new curriculum was taught in 8 weekly sessions by Clemson food safety and nutrition extension agents at sites randomized to the intervention.

Several challenges had to be met to implement this study. To reach the study population congregate meal sites were chosen as many elderly in SC regularly use these sites. This required a cluster randomized study design to allow most efficient use of the participants time and to avoid contamination among participants. A second challenge was posed by data collection. Because the study congregate meal sites were distributed throughout SC, use of a web-based database for immediate data entry would have been ideal. However, many older adults are not familiar with computers and have difficulty reading normal print size forms. As a compromise between use of technology and the pen-and-paper version, scannable forms with large print were developed to facilitate data entry. Due to participants low literacy levels, two or more extension agents were employed at each data collection session to minimize missing data by assisting with reading study questions. Additionally, all questions had pre-printed choices and did not require writing. A further challenge was posed by the time window for the 8 sessions set by the participants transportation services. In response, curriculum sessions were developed to fit within time constraints, as well as provide the participants with the information intended for each session in an easy-to-remember manner. Experiences with implementation of these solutions in this setting will be described.

**P09**

**INCORPORATING THE CURATION OF METADATA IN A DENTAL PRACTICE-BASED RESEARCH NETWORK**

Sherita Alai, Damon Collie, Don Vena, Tracie Lomax

*The EMMES Corp., Rockville, MD, USA*

In 2005, four dental Practice-Based Research Networks (PBRNs) were mandated to develop common means for the data sharing using tools developed by the National Cancer Institute Center for Bioinformatics (NCICB). The Practitioners Engaged in Applied Research and Learning (PEARL) Network, a National Institute of Dental and Craniofacial Research (NIDCR)-sponsored network of private-practice dentists, have utilized the Cancer Biomedical Informatics Grid (caBIG) to develop the capability to post clinical trial data for discovery and, possibly, also for de facto real-time transmission and storage of data from clinical trials.

In collaboration with the other Dental PBRNs, PEARL has developed metadata or Common Data Elements (CDEs) for all PEARL studies to date. After a study protocol has been developed, Case Report Forms (CRFs) are drafted and forwarded to PEARL s CDE Reviewer. The CDE reviewer then uses existing metadata and creates new meta-
data. Once all the metadata has been properly linked or created, the metadata version of the forms are created in the Cancer Data Standards Registry and Repository (caDSR) tool, Form Builder.

Using the expertise of NCICB and caBIG, PEARL is part of a larger data-sharing initiative, one based on identified standards, such as ISO 11179, the World Health Organization histologic classifications, and information and messaging models.

The goals of creating CDEs are inter-operability, data exchange and exposure, and basic scientific altruism. Currently, NIDCR, through the dental PBRNs, has made:
- 1524 Data Elements
- 1213 Data Element Concepts
- 318 Value Domains

PEARL has taken several steps to create harmonized, semantic metadata in order to utilize the collaborative nature of caBIG. PEARL has had success in reusing CDEs by standardizing parts or all of specific forms. Among the 1,524 CDEs created, there were at least 624 instances of CDE-reuse on CRFs.

**P10**

**THE PARKINSON'S PROGRESSION MARKERS INITIATIVE: A PROSPECTIVE BIOMARKERS STUDY**

Todd Sherer¹, Sohini Chowdhury¹, Mark Frasier², Jamie Eberling², Bernard Ravina², Andrew Siderowf³, Clemens Sherzer³, Danna Jennings⁵, Caroline Tanner⁶, Karl Kieburtz⁷, Christopher Coffey⁸, Arthur Toga⁸, Leslie Shaw³, John Q. Trajonoowski³, Ken Marek⁵

¹The Michael J. Fox Foundation for Parkinson’s Research; ²Biogen Idec, Inc.; ³The University of Pennsylvania; ⁴Brigham & Women’s Hospital; ⁵The Institute for Neurodegenerative Disorders; ⁶The Parkinson’s Institute and Clinical Center; ⁷The University of Rochester; ⁸The University of Iowa; ⁹Laboratory of Neuroimaging, University of California - Los Angeles

Parkinson’s disease (PD) interventional trials rely predominantly on outcomes that often vary within subjects and are not consistent across subjects. Reliable and well-validated biomarkers to monitor PD progression would dramatically improve patient care and accelerate research into both PD etiology and therapeutics. During the past two decades much progress has been made in identifying and assessing PD biomarkers, but as yet, no fully validated biomarker for PD is available. Given the recent advances in molecular genetics, neurobiology, imaging technology, and radiochemistry that have provided new tools that may be useful for PD biomarkers, and the recognition that the lack of PD progression biomarkers has created a roadblock for further studies of disease modifying therapies, there is increasing consensus that a major initiative to develop PD progression biomarkers is both necessary and feasible.

In 2010, the MJFF launched the Parkinson’s Progression Markers Initiative (PPMI) - a large clinical study that will enroll 400 PD subjects and 200 healthy controls with the objective to collect clinical, imaging, and biologic data to develop biomarkers of Parkinson’s disease progression. The data will be collected over 3-5 years and will include motor and non-motor clinical data, dopamine scans, and biological fluids (blood, urine, cerebral spinal fluid) collection. Clinical and imaging data will be made available to the PD research community; researchers will be able to apply for access to the stored biologic samples. A portion of collected samples will be used to verify promising biologic analytes. This initiative will create a consortium of academic centers, government agencies, PD foundations, and pharmaceutical and biotech companies. The ultimate goal of this initiative is to identify progression biomarkers that may accelerate neuroprotection and neuroprevention studies of PD therapeutics.

**P11**

**EFFICIENT MANAGEMENT OF DIVERSIFIED FUNDING WITHIN THE GYNECOLOGIC ONCOLOGY GROUP (GOG) STATISTICAL AND DATA CENTER (SDC)**

Sally Bialy, Jennifer Reed, Melissa Seifert, John Blessing

Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, USA

The structure of Cooperative Group funding changed substantially over the past decade. The GOG was predominantly funded through National Institutes of Health (NIH) federal grants from its inception in the mid 1970s through the 1990s. However, during the first decade of the 21st century, the GOG was faced with flat NIH funding and therefore began to diversify its financial portfolio in order to maximize resources to fund clinical research aimed at promoting excellence in clinical and basic scientific research in the field of gynecologic malignancies. During this same period, the GOG broadened its fiscal configuration to strengthen involvement in diverse areas.
of investigation such as translational research, tissue banking, bioinformatics, cancer prevention and control, and quality of life. In 2000, the SDC managed four grants and contracts. In 2010, there are over 100 proposed or funded budgets comprised of NIH grants, subcontracts with GOG Institutions, and contracts with industry partners. The SDC developed finance and contractual management systems to accommodate this paradigm shift from a small number of large funding sources to a large number of funding sources which include numerous specific projects with associated funds. A team strategy is used to efficiently develop budgets that are increasingly complex in order to support innovative and novel ideas. Accurate acquisition and disbursement of the resulting stratified funding has necessitated the development of complimentary accounting systems. Moreover, fulfillment of contractual obligations at multiple time points required the development of complicated tracking systems. The SDC has developed a series of budget development, accounting, and tracking systems to efficiently manage the diversification of funding sources necessary to support GOG research.

**P12**

**RISK RATIO VERSE ODDS RATIO IN CLINICAL TRIALS OF BINARY OUTCOMES**

Kellee M. Miller

*Jaeb Center for Health Research, Tampa, FL, USA*

The primary outcome in clinical trials is often estimating the risk of a binary outcome in one group compared with the risk in another group. The purpose of this study was to assess the advantages and disadvantages or reporting the risk ratio (RR) instead of the odds ratio (OR) in clinical trials of binary outcomes and to demonstrate several effective methods for obtaining the risk ratio using SAS version 9.2 software. The RR is the only measure that truly estimates cumulative incidence risk over a period of time. The OR overestimates the risk ratio, unless the outcome is rare; which is often not the case in many clinical trials. Graphical representations of the relationship between OR and RR at various incidence levels of the outcome show that for an outcome incidence of 30%, an OR of 4.0 corresponds to a RR of less than 2.0. An advantage of the OR is that the estimate obtained from modeling the presence of an outcome is the reciprocal of the estimate obtained from modeling the absence of an outcome.

The most common methods for obtaining the RR are the log-binomial model and the modified Poisson regression model, both of which can be estimated using the SAS PROC GENMOD procedure. The log-binomial model is theoretically a better model and has been shown to be more efficient; however practical illustrations of this model have produced common convergence problems.

The OR is often misinterpreted by clinicians as a measure of risk. There are now several ways for obtaining the RR. Clinical trial researchers should consider reporting the RR instead of the OR to avoid misinterpretation with respect to the magnitude of treatment effect.

**P13**

**TESTING LIPID TREATMENT EFFECTS IN THE PRESENCE OF SKEWED DATA CAUSED BY OFF-THERAPY DISCONTINUATION VALUES**

Aditi Sapre, Thomas Cook

*Merck & Co., Rahway NJ, USA*

In lipid studies where patients are on a stable dose of lipid-lowering medication at baseline, patients who discontinue study therapy and fail to provide a discontinuation blood draw within a short time span will be largely washed off their statins at the end of study visit. Typically, these “dropout” patients will experience a lipid rebound with their lipid values returning to pre-statin levels (which could be as high as 70% above their baseline on-statin levels). This problem is further compounded in studies where the proportions of dropouts are high and differ markedly across treatment groups. Using conventional parametric analysis techniques to test the between treatment effect in the presence of these influential observations caused by the “gap” (length of time between discontinuation of therapy and lipid measurement) may provide misleading and biased estimates of the treatment effect. The focus of this research is to investigate the properties of statistical methods that overcome the influence of the rebound measurements. Simulations under varying dropout and gap patterns were performed to compare the properties of analysis methods like ANOVA using LOCF, ANOVA using LOCF on ranks, Last valid value carried forward (actual value and ranks), Composite Shih/Quan test, constrained LDA on logs and repeated measures analysis. Results of the assessment of these methods show that they all provided adequate control.
of the Type 1 error rate and that the rank based approaches failed to provide a significant advantage compared to the analysis methods on actual values.

**P14**

**EVENT ADJUDICATION OF VISUAL FIELD ENDPOINTS IN THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS)**

Mae Gordon, Dale Heuer, Eve Higginbotham, Richard Parrish, Patricia Morris, Bradley Wilson, Julie Beiser, Michael Kass for The Ocular Hypertension Treatment Study

Washington University School of Medicine, St. Louis, MO, USA

Visual field loss is the primary outcome measure accepted by the FDA for clinical trials of drugs to prevent or to treat glaucoma. Many ocular and systemic conditions can cause visual field loss. In the Framingham Eye Study, the prevalence of other ocular conditions capable of causing visual field loss (cataract 12.3%, age-related macular degeneration 5.7% and diabetic retinopathy 1.8%) collectively far exceed the 1.9% prevalence of open angle glaucoma. Stroke, which can cause visual field loss, has a prevalence of 8.1% among individuals 65 years and older. The Ocular Hypertension Treatment Trial (OHTS), is a randomized clinical trial of the safety and efficacy of topical ocular hypotensive medication in the prevention of primary open angle glaucoma (POAG). OHTS is only National Eye Institute trial of glaucoma to use an Event Adjudication Committee. We report the impact of event adjudication on estimates of POAG incidence, treatment efficacy and statistical power. Of the 1,636 participants randomized, 132 developed a visual field endpoint. Of the 132 visual field endpoints, 49% (65 of 132) were attributed to POAG, 51% (67 of 132) to other causes. The incidence of POAG was 4.0% (65 of 1,636) with adjudication and 8.1% (132 of 1,636) without adjudication. The relative risk for treatment benefit was 0.71 (95% CI of 0.60 to 0.84) with adjudication and 0.87 (95% CI of 0.74 to 1.01) without adjudication. Post-hoc statistical power estimated by a proportions test for independent samples was 0.88 with adjudication and 0.37 without adjudication. Event adjudication reduced bias in estimates of POAG incidence and treatment benefit as well as increased statistical power.

**P15**

**SUPPLEMENTING THE ONCORE CLINICAL RESEARCH MANAGEMENT SYSTEM WITH A WEB-BASED BLINDED RANDOMIZATION MODULE FOR INVESTIGATOR INITIATED ONCOLOGY TRIALS**

Brent Shelton, Emily Van Meter, Stacey Slone, Li Li, Isaac Hands, Heidi Weiss, Steve Sitzlar, John Hayslip, Susanne Arnold, John Rinehart

University of Kentucky Markey Cancer Center Lexington, KY, USA

The OnCore Clinical Research Management System designed by Forte Research Systems does not permit trials to implement blinded randomization. This work describes efforts by University of Kentucky Markey Cancer Center biostatistical, clinical, and pharmacy staff to supplement the OnCore system with a web-based randomization module in an effort to provide blinding and real-time access when randomizing patients to investigator initiated oncology trials. Methods The design for this module requires the biostatistician assigned to a protocol to first develop an electronic list with the randomization assignments corresponding to clinical protocol design specifications. This list is then uploaded to a MYSQL relational database which is available at the time the study pharmacist requests a randomization assignment for a protocol. Access to this randomization module for study pharmacists and biostatisticians occurs through a secure, encrypted connection. This module permits the biostatisticians to view: (a) all blinded oncology protocols (b) randomization code lists (c) patient assignments that have been made and (d) log files describing randomization-related transactions. Biostatistician users cannot add new patients or randomize them to any oncology protocol. Protocol pharmacists can: (a) view only their assigned protocols (b) view patient randomized assignments only for their assigned protocols and (c) add new patients to their assigned protocols. Pharmacists cannot view complete randomization code lists or access transaction log files. Discussion It is anticipated that supplementation of OnCore with this blinded randomization module will facilitate the blinding process in all investigator initiated oncology trials at our center. It is also hoped that the OnCore facilitators may find our module design useful enough to pursue implementation of all or even part of it in future releases of this important oncology trial management software that is now widely used at other cancer centers in the US and abroad.
ACHIEVING COMPLETE AND CLEAN DATA IN PREPARATION FOR DATA ANALYSIS

Sunny Chan, Michael Shi, Elizabeth Asztalos

The Centre for Mother, Infant, and Child Research Sunnybrook Research Institute Toronto, Ontario, Canada

For randomised controlled trials (RCTs), incorrect or incomplete data often have negative implications in the publication of results. There are several reasons for incorrect or incomplete data including user entry errors, data loss and missing information. Therefore, it is essential to have a verification process to detect these problems during a trial, especially during any analysis phase. The Centre for Mother, Infant, and Child Research (CMICR), is the data and clinical coordinating centre for several multicentre RCTs. Data collected at CMICR must be validated against a comprehensive set of criteria programmed to capture and eliminate logic errors. Moreover, there are programs designed to track when data forms are expected to arrive at CMICR based on specific clinical procedure timelines.

During the analysis phase, monthly reminders list all data booklets and queries that are immediately due and must be sent to the data coordinating centre as soon as possible. Advanced reporting programs are designed using SAS software and Microsoft Access to target specific sites with missing case report forms and overdue queries. Specifically, we have designed and implemented a complete and clean data reporting program to compute the overall progress of data collection for all recruiting sites as well as for the trial.

The trial coordinating team is actively contacting the site investigator and coordinator to collect case report forms and clarify all patient data queries. With the reporting programs available on demand, the trial coordinator at CMICR can easily monitor the status of every patient recruited. This approach has been implemented for several RCTs at CMICR, successfully ensuring a complete and clean dataset for analysis.

PROCESSES IMPLEMENTED TO ENSURE SUCCESSFUL FOLLOW-UP DURING ONGOING RECRUITMENT

Kathryn Mangoff, Dalah Mason, Sonya Mergler, Johanna Sanchez, Jon F.R. Barrett, Elizabeth Asztalos

The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Toronto, Ontario, Canada

The Twin Birth Study (TBS) is an international multicentre randomised controlled trial with 97 actively recruiting centres in 25 countries with a recruitment goal of 2800 patients. TBS 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. Recruitment is expected to end in 2011 and follow-up will be completed 2 years after the last patient has been randomised. The follow-up component determines the secondary outcomes and consists of women completing questionnaires at 2 years postpartum, and an assessment of the neurodevelopmental outcomes of the children at 2 years corrected age.

The TBS protocol projects greater than 80% follow-up rate and therefore, is important to remind centres to complete follow-up even while recruitment is ongoing. To achieve this, specific processes have been implemented. On a monthly basis centres receive a “Maintaining Contact” report listing specific intervals in which they should contact patients, and a “2 Year Follow-Up” report listing patients that are about 21 months postpartum and are required to complete the questionnaires. Procedure forms are attached to these reports demonstrating how to accurately complete the questionnaires. Additionally, in November of each year centres are mailed their follow-up supplies for the upcoming year. Finally, a follow-up table is included in a monthly newsletter so centres can track their progress.

As of November 2010, these processes have been successful in achieving a follow-up rate of 85.2%, for patients recruited up until the end of 2007.
P18

THE LIFESTYLE INTERVENTIONS AND INDEPENDENCE FOR ELDERS (LIFE) INTERVENTION TRACKING SYSTEM: MONITORING TREATMENT FIDELITY AND PROMOTING BEHAVIOR CHANGE

Wesley A. Roberson¹, Delilah R. Cook¹, Roger A. Fielding², Jeffrey A. Katula¹, Shannon L. Mihalko¹, Michael E. Miller³, Michael P. Walkup¹, W. Jack Rejeski¹

¹Winston-Salem, NC, USA; ²Boston, MA, USA

The LIFE study is an 8-site multi-center RCT (n = 1600) examining the effect of a physical activity intervention versus a successful aging control treatment on major mobility disability as defined by failure to complete a 400-m walk. All participants will be randomized to treatment for a minimum of 2 years. A unique feature of LIFE has been the development of a web-based intervention tracking system that has 4 goals: (1) to provide dynamic reports of attendance, physical activity, and self-monitoring used by the intervention committee to monitor treatment fidelity; (2) to provide a database of participants medical and psychosocial profiles that intervention staff can use to enhance staff/participant interactions and allow for the tailoring of treatment; (3) to generate dynamic reports that are used by interventionists to monitor and provide feedback on the progress of their participants; and (4), to serve as a platform for posting written materials and videos that facilitate standardized delivery of the intervention and the sharing of strategies for promoting desired behavior. These goals are accomplished through use of an interactive web-user interface built with Adobe Cold Fusion with a Microsoft SQL Server database. SAS and SAS/IntrNet is used to program dynamic reports that track attendance and physical activity levels. The tracking system is based on a social cognitive framework for self-management.

P19

MISSING COVARIATE DATA WITH A SURVIVAL ENDPOINT: PROBLEMS AND SOLUTIONS PERTAINING TO DESIGN, DATA COLLECTION AND ANALYSIS

Donna Elise Levy¹, Annette Dalton², Steve Gilbert¹, Daniel Joe Quinn³

¹Rho Inc., Chapel Hill, NC, USA; ²Dana-Farber Cancer Institute, Boston, MA, USA; ³Partners Healthcare, Boston, MA, USA

Missing data is a problem that can arise in any type of clinical investigation. As has been reported, studies with missing data result in decreased power, loss of information and can be biased, thus leading to inaccurate and potentially incorrect conclusions.

During the planning process, study objectives need to be considered in order to build an appropriate plan which will ideally ensure quality data, analyses and results. This includes protocol development, case report form design and statistical analysis plan and how all are interconnected. Also considered are the participating institutions, data management, investigator, laboratory, statistician and patient all working together, directly and indirectly in order to limit missingness and attain the objectives of the study. Site training and communication throughout the duration of the trial, as well as timely data quality control, are all key components.

However, even with the best planning, some missing data may be unavoidable. Statistical methods and software dealing with missing data are becoming more prevalent. Nonetheless, complete or available data methods appear to be the prominent analyses performed and included in trial publications. Even when data is missing completely at random or missing at random, the effects on the analysis and conclusions can be significantly affected.

We will discuss methods of avoiding missing data that can be incorporated into every phase of the clinical trial. We will also review the results of multiple analysis techniques in the presence of missingness found in prognostic factors with a survival endpoint. In addition, we will address methods of assessing patterns of missingness. An overview of common statistical packages with missing data procedures as well as underlying assumptions will also be addressed.
P20
RANDOMIZATION ISSUES IN A RANDOMIZED MULTI-CENTER TRIAL OF AN EDUCATIONAL INTERVENTION FOR IMPROVING GLUCOSE CONTROL IN PATIENTS WITH DIABETIC RETINOPATHY
Jaeb Center for Health Research, Tampa, FL, USA, Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231 and EY14269.

Purpose: To explore the potential issues and solutions related to randomization when designing a randomized multi-center educational intervention trial Background: The primary objective of the Effect of Diabetes Education during Retinal Ophthalmology Visits on Diabetes Control Study is to determine whether diabetes education in the ophthalmology office can improve glucose control assessed with hemoglobin A1c (HbA1c) levels as compared with standard care in the ophthalmology office. Design: Several randomization options were considered including randomization by participant, by investigator, or by clinical center. These various options impact the study sample size, which is always an important consideration when designing a trial. Although randomization by participant would result in the smallest sample size, the approach was not considered ideal due to concerns about potential bias which could be introduced to standard care participants by an investigator also administering the educational component to intervention participants. Concerns with randomization by investigator or clinical site include potential imbalances between the types of populations served which have a relationship with the outcome of interest (HbA1c). Thus, balancing groups by characteristics that might impact treatment effect, such as age, education, socio-economic status, and race/ethnicity was an important consideration with these randomization options. Ultimately, a cluster randomization design was implemented using a combination of randomization by clinical center at centers with only one participating investigator and by investigator within center at centers with multiple investigators.

Conclusions: Cluster randomization is appealing when designing a trial where there is concern about treatment group contamination. However, factors that may affect the outcome of interest should be prioritized and taken into account prior to establishing the randomization approach.

P21
METHODS IN PROMOTING A CLINICAL RESEARCH TRIAL
Dalal Mason, Sonya Mergler, Johanna Sanchez, Jon F.R. Barrett, Elizabeth Asztalos
The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Toronto, Ontario, Canada

The Twin Birth Study (TBS) is an international multicentre randomized controlled trial (RCT) with 97 participating centers in 25 countries. The study seeks to determine 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. TBS has a recruitment goal of 2800 patients and an estimated 120-150 international centers requirement. Our goal as the Data Coordinating Centre at the Centre for Mother, Infant, and Child Research, was to encourage additional sites to join TBS, and to continually advance patient recruitment at participating sites, such that our recruitment goal would be met and to make available the answer to this important question.

Promoting a study to raise awareness will result in an increase in centre participation and participant interest - and therefore will increase patient enrollment. Creating promotional items, posters, educational DVDs, patient and physician brochures, features in magazines, hosting collaborative meetings, and personal contacts are just some examples of ways to feature a study. With all study advertising, applicable local and international regulations and requirements must be considered. TBS applied these and other promotional strategies throughout the duration of the study with great success in both an increase in centre participation and a surge in recruitment.

Awareness and enthusiasm for a trial is imperative for successful recruitment. This presentation will offer some methods of advertising a study in order to promote and raise awareness, thereby raising the potential for recruitment.
UNMASKING PATIENTS WHILE MINIMIZING BIAS IN FUTURE FOLLOW-UP STUDIES
Marlene Leung, Mariam Saleem, Johanna Sanchez, Elizabeth Asztalos
Sunnybrook Research Institute, Ontario, Canada

The Multiple courses of Antenatal Corticosteroids for preterm birth Study (MACS), was an international, multi-site randomised controlled trial which examined the effects of repeat courses of antenatal corticosteroids on adverse perinatal/neonatal outcomes. MACS completed recruitment in 2006 with a total of 1858 women enrolled. In MACS-5, the children are examined at five years of age, for any impairment of their neuromotor, neurosensory and neurocognitive function. While MACS-5 is expected to finish by mid 2011, there is the possibility of another follow-up study to be conducted on the original MACS children at a later age. However, between the final stages of MACS-5 and the start of a longer follow-up study, several sites contacted the coordinating centre with patient requests to be unmasked.

To manage unmasking requests, a series of organizational and administrative procedures were established. First, the coordinating centre polled participating sites to gauge the feasibility of another follow-up study. Upon positive poll results, sites were notified to contact MACS families about their participation. Finally, a programmer who is not directly involved with the trial was given access to the locked allocation database.

When an unmasking request is received, the following steps are followed: a) the programmer merges patient allocation information into a form letter and places it in a sealed envelope, b) the envelope is sent to the participating site with instructions to send it directly to the family and c) a log of unmasked patients is updated and access is restricted.

This process allows the coordinating centre to manage patient requests to be unmasked, without unmasking involved trial staff. It also protects against bias for potential future follow-up studies.

STRATEGIES IMPLEMENTED TO ACHIEVE THE FOLLOW-UP GOAL IN A 5-YEAR FOLLOW-UP STUDY
Mariam Saleem, Johanna Sanchez, Elizabeth Asztalos
The Centre for Mother, Infant, and Child Research Sunnybrook Research Institute, Toronto, Ontario, Canada

Multiple courses of Antenatal Corticosteroids for preterm birth Study: A 5-year Follow-up (MACS-5), is an international multicentre trial that follows the MACS children to 5 years of age to determine the long-term effects of antenatal corticosteroids with emphasis on cognitive, behavioural and motor development.

MACS completed recruitment in August 2006 with 1858 women enrolled from 80 centres, and completed the 18-24 month follow-up component April 2009. It was anticipated that approximately 80% of these MACS centres would participate in MACS-5, and that about 80% of the women recruited at each centre would consent to the assessment of their children; therefore we anticipated completion of 1200 assessments by December 2011.

Centres received several reminders: the first was upon completion of the MACS 18-24 month follow-up component, reminding them to remain in contact with the children; and the second and third were at intervals closer to their 5th birthday, reminding them to schedule the assessments. Centres received trial information through MACS-5 monthly newsletters, site visits, and small regional meetings. Due to some mobile populations, as well as challenging centres, MACS-5 faced some difficulties with data retrieval. Therefore, efforts to retrieve data were increased and specific strategies were implemented.

Mobile patients were contacted by their primary centre and relocated to an alternative MACS-5 centre closer to the patient to complete assessment. If this was not possible, a local collaborator conducted house visits. Challenging centres were frequently contacted by email, and followed up with a phone call. Continued delays in receiving data lead to the implementation of a pre-arranged courier pick-up of data from the centres. This proved to be a successful method and more cost-effective than site visits.

These strategies were successful in achieving the targeted goal of 1200 assessments one year prior to the study completion date.
P24
THE IMPACT OF SUBSTANTIAL CASE REPORT FORM MODIFICATIONS
POST DATABASE LAUNCH IN A MULTI-CENTER DATA REGISTRY
Danielle Johnson, Traci Clemons, Donna Brown, Nancy Jones
The EMMES Corporation, Rockville, Maryland, U.S.; Autism Speaks, Los Angeles, CA, USA

The Autism Treatment Network (ATN) Registry, sponsored by Autism Speaks, is a multi-center registry for 14 U.S. sites and 1 Canadian site. These sites are to enroll 100 participants with Autism Spectrum Disorder (ASD) (ages 2-17) per year and follow enrolled participants for three years. ASDs are complex neurodevelopmental disorders characterized by impaired social interaction, delayed and disordered language, and repetitive/stereotypic behaviors. The current prevalence rate of ASD among children in the U.S. is one in 110. The goal of the ATN Registry is to characterize ASD child healthcare needs and inform development and guidelines of their medical care. During Year 1 of the Registry, 10 customized ATN Registry case report forms (CRFs) were used as a standard battery of care. The eCRFs were developed in the secure web-based data capture system provided by The EMMES Corporation.

At the end of Year 1, the ATN battery was reviewed and the CRFs were modified per ATN clinician input. The CRFs were piloted at all sites prior to development of the eCRFs which were then piloted as well. The eCRF modifications required updating; dividing into multiple eCRFs; data dictionary and code list modification and generation; and significant field mapping. A total of 17 eCRFs were modified, including two that were split to create two additional eCRFs, and four new eCRFs were created requiring the mapping of 448 fields. The project team identified multiple lessons learned as well as barriers faced during the database modification process including: creating a tighter timeline, establishing a working group for CRF review, limiting the sites in the pilot, and decreasing the need for field mapping by “recycling” eCRFs.

P25
MAKING MEETING SCHEDULING MORE EFFICIENT, SIMPLE, AND RELIABLE:
USING KAI’S WEB-BASED SHARED CALENDAR APPLICATION
Ben Piper, Stephanie Millin, Tiffany Abushaikha, Patti Shugarts, Rene Kozloff
KAI Research, Inc., an Altarum Company, Rockville, MD, USA

Efficient communication and scheduling are key factors in the execution and fluidity of clinical studies. KAI is frequently contracted by the NIH and commercial clients to schedule meetings for Data Safety Monitoring Boards (DSMBs), Steering Committees and other ad hoc meetings. This at times can be quite challenging with participants schedules so demanding.

To facilitate this process, KAI embarked on the design and implementation of a Web-based communication and scheduling system known as the KAI Shared Calendar (SC). Our goal was to evaluate and improve the scheduling process by developing an automated, web-based system that decreases administrative burdens while allowing users to communicate their schedules quickly.

Challenges: Prior to the SC, KAI used a combination of paper-based calendars and emails to schedule meetings, a time consuming approach, mostly due to the inability to quickly collate the data received.

Solution: We reviewed many online scheduling applications, but chose not to use an existing application due to security and reliability concerns. We designed an application that makes it simple for invitees to submit their availability and allows coordinators to better organize and automate the scheduling process. The final SC features:

• Simple drag and drop date selection (exhibit 1)
• Storage of invitee names and email addresses
• Pre-programmed email reminders/notifications
• Meeting invite embedded into attendee’s calendar (Outlook, iCal, etc.)

Conclusions: Following implementation of the SC we saw a dramatic increase in scheduling efficiency and increased participant satisfaction as seen in the metrics below comparing SC with paper calendar use:

• 30% fewer emails sent when scheduling a single meeting
• Reduced average Invitee response time from 4 days to 2.
• Reduced average time to finalize a meeting from 21 days to 10
P26
CREATING A DIGITAL LIBRARY FOR GYNECOLOGIC ONCOLOGY GROUP (GOG) MANUSCRIPTS UTILIZING THE STATISTICAL AND DATA CENTER (SDC) INFORMATION TECHNOLOGY INFRASTRUCTURE
Melissa Leventhal, Sally Bialy, William E. Elgie, John Blessing.
Gynecologic Oncology Group Statistical and Data Center, Buffalo, New York

Since its inception in 1970, the GOG has contributed over 650 manuscripts to peer reviewed journals. The GOG publications function is uniquely positioned within the SDC. One of the many dividends of this arrangement is the availability of sophisticated information technology systems. Initially, a publications database was developed to collect bibliography data and more recently Group wide tools have been created to support GOG Investigators. In anticipation of journals providing electronic links for manuscripts, fields were added to accommodate them and the Group was able to take immediate advantage of this technology. To compliment this upgrade, a database search tool was created for the GOG Member Website which allowed investigators to use an array of variables to search for manuscripts or abstracts, and then use links for journal/article access. However, since electronic links to journals did not exist until 2000, over fifty percent of GOG manuscripts, many of which are the foundation for current research, were only available as paper reprints. In order to better serve the archival functions of the GOG, this print collection was digitized. After manuscripts were converted to a digital format, PDF OCR (Optical Character Recognition) was utilized to accommodate searches within individual documents. The publications search engine was revised to incorporate hyperlinks to corresponding text. Using the existing search engine to add the digitally archived publications enhanced the search options already available, including by author, protocol, keyword, etc. The collection resides as a secured file on a GOG web server. Access is restricted through password protection and encryption to ensure compliance with copyright and fair use laws.

P27
DESCRIPTION OF THE IMPLEMENTATION AND EXECUTION OF THE SECONDARY PREVENTION OF SMALL SUBCORTICAL STROKES STUDY (SPS3) PROMOTED BY THE NIH IN SPAIN
Martin, A.1, Sanllorente, M.1, Roldan, A.2, Rosso, CM.1, Benavente, O.2, Manriquez, M.1
1Clinical Trials Unit, Hospital Universitario de Bellvitge. Fundación Idibell. Barcelona, Spain; 2University of British Columbia, Vancouver, BC, Canada.

The Secondary Prevention of Small Subcortical Strokes study (SPS3), funded by the NIH, was initially intended to be implemented solely at American clinical sites. However, due to an unanticipated shortfall in patient recruitment, the study was approved for operation at international sites including Spain.

To conduct a clinical trial in Spain the trial investigators must comply with local laws and delegate responsibilities to a legal representative. In this case, the foundation of a public hospital was chosen. The Clinical Trials Unit (CTU) linked to the foundation assumed the functions of the Coordinating Center in Spain, including administrative and regulatory management, contact with the national regulatory agency and IRBs, site coordination, randomization and data entry, communication with the sponsor and relevant committees, and medication management.

The CTU was responsible for selecting participating sites and carrying out relevant arrangements for trial induction. It obtained approvals from regulatory authorities and the IRBs, selecting one as the reference IRB who acted as the liaison for other participant sites. Once the approvals and required documentation were obtained and the research team was trained according to SPS3 protocol, patient recruitment was authorized and commenced. The interval between initial site preparations and patient enrolment was approximately one year.

Once sites are operating, it is the responsibility of the CTU to perform the randomization of patients, enter the data, and perform monitoring visits as required. It is also the intermediary between the sponsor and the sites, as well as the primary contact with the national regulatory agency and IRBs regarding submission of annual reports, communication of relevant modifications, and notification of serious and unexpected adverse events. Another key duty of the CTU is the management of the importation of trial medication and its distribution through the appropriate channels.
TWENTY FOUR MONTH OUTCOMES OF RANDOMIZED EQUIVALENCE TRIAL OF TWO SURGICAL TECHNIQUES FOR WOMEN WITH STRESS URINARY INCONTINENCE: RETROPUBIC AND TRANSOBTURATOR MIDURETHRAL SLINGS (TOMUS)
New England Research Institutes, Watertown, MA, USA; University of California, San Diego; University of Texas, Southwestern; University of Alabama at Birmingham; University of Maryland; Loyola University; University of Texas, San Antonio; William Beaumont Hospital; Magee-Women’s Hospital; University of Utah; Dartmouth-Hitchcock Medical Center; National Institute of Diabetes and Digestive and Kidney Diseases

INTRODUCTION AND OBJECTIVES: Transobturator (TMUS) and retropubic (RMUS) midurethral slings are common surgical techniques for women with stress urinary incontinence (SUI). Because we had no preconceived notion of which approach would have better long-term efficacy, instead of a non-inferiority trial, we assessed 24 month outcomes in a randomized equivalence trial of TMUS and RMUS. METHODS: Primary outcomes were objective and subjective SUI cure rates at 12 and 24 months post surgery. 12 month outcomes were reported (NEJM 362:2206, 2010) previously. Objective cure was defined as a negative stress test, negative pad test and no retreatment; subjective cure was defined as absence of SUI symptoms, no leakage on 3-day bladder diary and no retreatment. An equivalence margin of +/- 12% was established a priori. The primary analysis for equivalence was per protocol (assigned surgery performed); all other analyses were intention-to-treat. Secondary outcomes included persistent or de novo urge incontinence, voiding dysfunction, mesh complications, patient satisfaction, and quality of life. RESULTS: Objective success rates for RMUS and TMUS were 77.3% and 72.3% respectively, (95% CI for difference of 5.1%: -2.0, 12.1%) and subjective success rates were 55.7% and 48.3% (CI for difference of 7.4%: -0.1%, 15.5%). Both tests for equivalence were inconclusive. No differences were found between the groups regarding patient satisfaction, quality of life, de novo or persistent urge incontinence or mesh exposure. The RMUS group had higher rates of voiding dysfunction requiring surgery and urinary tract infections while the TMUS group had higher rates of neurologic symptoms. CONCLUSIONS: While objective outcomes were equivalent between RMUS and TMUS at 1-year, 24 month objective and subjective cure rates did not meet predefined criteria for equivalence. Patient satisfaction remained high and symptom severity remains markedly improved over baseline for both groups. No additional AE differences between the groups were identified.

AN ASSESSMENT OF DIFFERENT METHODS FOR CALCULATING CONFIDENCE INTERVALS ON PROPORTIONS
Mark Schactman, Alicia Toledano
Washington, DC, USA

Computing confidence intervals on proportions is relatively easy, but computing the correct confidence interval is hard. If the sample size is large and the proportion is not too close to either end of the natural boundaries of zero and one, the normal approximation (with or without continuity correction) works well (i.e., has proper coverage). For smaller sample sizes, the exact method of Clopper and Pearson is often used. This method provides accurate results if the proportion is not too close to the boundaries.

In some situations, the proportion of interest is close to zero or one. For example, consider an assay with sensitivity and specificity values above 0.95. If the goal is to estimate the one-sided 95% lower confidence bound, care must be taken to ensure an accurate estimate and appropriate coverage. On the other extreme, consider estimating the confidence bound for a rare adverse event that occurs in less than 1% of subjects. How should we estimate the one-sided upper bound of our confidence in this case?

This poster will compare the Clopper-Pearson, Wilson score, mid-P, and Blyth-Still-Casella intervals. Details on implementation of these methods will be provided along with tables and figures that will allow direct comparison of the results. Metrics will include percent coverage and comparison of confidence bounds for different sample sizes. Results will draw on previous work done by Vollset (Statistics in Medicine, 1993), Newcombe (Statistics in Medicine, 1998), and others.
P30
THE BENEFITS AND CHALLENGES OF UTILIZING A EUROPEAN CRO TO FACILITATE MASTER FILE MAINTENANCE, HEALTH AUTHORITY SUBMISSIONS, AND ON-SITE MONITORING FOR AN INTERNATIONAL CLINICAL TRIAL
Traci Schwieger, Deb Feddersen
The University of Iowa, Clinical Trials Statistical & Data Management Center; Iowa City, IA, USA

When conducting a clinical trial in a foreign country, a local Contract Research Organization (CRO) can provide the necessary expertise to collect and review regulatory documents, perform site monitoring visits, and submit required documents to the European Health Authorities. The University of Iowa Clinical Trial Statistical Data Management Center (CTSDMC) functioning as the data coordinating center for the NIH-funded international Clinical Islet Transplant Consortium (CITC) trials utilizes a Nordic CRO to maintain protocol and regulatory compliance of the clinical trial in Norway and Sweden. In collaboration with the Nordic CRO, we developed Project Work Instructions (PWIs) that establish regulatory and clinical guidelines for the following: 1) Nordic Network Communication Plan; 2) Nordic Site Initiation Visits; 3) Nordic Interim Monitoring Visits; 4) Clinical Study/Regulatory Document Review; and 5) Submissions to the European Health Authorities. Clinical and regulatory issues, along with the PWIs, are reviewed regularly on teleconferences with the NIH, CTSDMC, Nordic clinical sites and the Nordic CRO. Having the expertise of the Nordic CRO has proved beneficial in a variety of ways: 1) they are in direct contact with the sites to collect and maintain required documents; 2) they are familiar with European guidelines and are instrumental in ensuring compliance; and 3) they complete the required applications, updates, and annual reports to the European Health Authorities in the native language. While a local CRO is beneficial in facilitating clinical and regulatory processes, it also has its challenges. For example, the Nordic CRO has previously established standard operating procedures that differ slightly from the clinical and regulatory processes required for a NIH-funded study. This presentation will describe several challenges and the steps we took to overcome them. We will also further describe our procedures, and provide suggestions for others who are thinking about working with a foreign CRO during international studies.

P31
THE SECONDARY PREVENTION OF SMALL SUBCORTICAL STROKES STUDY EXPERIENCE AT INTERNATIONAL SITES
Robert Hart1; Jeff M. Szychowski2; Kalyani Peri2; Robin Conwit3; Oscar Benavente4
1University of Texas Health Science Center at San Antonio; San Antonio, TX, USA; 2University of Alabama at Birmingham; Birmingham, AL, USA; 3National Institute of Health (NIH/NINDS); Bethesda, MD, USA; 4University of British Columbia, Vancouver, British Columbia, Canada

Our objective is to share our experiences conducting the Secondary Prevention of Small Subcortical Strokes (SPS3) study, a U.S. NIH/NINDS sponsored trial, at international sites (Latin America and Spain). SPS3 is a randomized, double-blind, multicenter study focused on recruiting patients with symptomatic lacunar strokes within the prior 6 months, verified by an eligible lesion on MRI from specific, understudied populations. Participants are simultaneously randomized in a 2-by-2 factorial design to two interventions: antiplatelet therapy (aspirin 325 mg plus clopidogrel 75 mg daily versus aspirin 325 mg plus placebo daily, double-blind ) and to two levels of systolic blood pressure targets (Intensive: <130 mmHg versus Usual: 130-149 mmHg, Open Label ). The aim of the study is to reduce stroke recurrence, cognitive decline and major vascular events. Recruitment commenced on March 2003 at 35 sites located in the U.S. Because of difficulties achieving the monthly recruitment goals, the SPS3 consortium required additional members. Sites in Latin America and Spain were invited to join, and the study is currently being conducted at 70 sites in 8 countries. This new facet of the study presented a unique set of challenges in conducting the trial, including different regulatory requirements, costs, geographical localization, etc. By including Latin America and Spain in the SPS3 consortium, the benefits for a large multi-center trial of international site operation in terms of fiscal viability, recruitment, compliance to protocol and procedures, and data quality can more than compensate for the financial effort and modifications in the day-to-day management of an international cohort. Principal Investigator: Oscar Benavente, MD Professor of Neurology at UBC, Vancouver, BC. Canada Trial registration: NCT00059306 Grant #: U01 NS38529
Conducting clinical trials in substance abuse populations presents many challenges. Huge strides have been made over the last 35 years in advancing the use of scientific strategies to treat and prevent addiction including a combination of pharmaceutical and behavioral approaches provided through community level clinics. For the last 11 years, KAI has served as the Data Management and Coordinating Center for more than 20 phase I and II studies sponsored by the National Institute on Drug Abuse (NIDA). Through this work we have identified many obstacles in recruiting and retaining compliant participants into studies and had the opportunity to implement and optimize solutions.

This presentation will provide information on the complex challenges faced by those conducting substance abuse treatment and recovery trials as detailed below:

* Issues in performing multi-site studies
  - Regional population differences in:
    § Substances of abuse
    § Receptiveness to behavioral vs pharmacologic treatments
  - Community-based vs academic clinics
  - PI oversight and study staff turnover

* Ethics of inclusion
  - Consent under the influence
  - Behavior or report changed to conform to eligibility criteria

* Recruitment & retention
  - Targeting advertising
  - Trends in substance use
  - Exclusionary co-morbid conditions
  - Participant time commitment

* Protocol compliance
  - Investigational product
  - Attendance at visits
  - Self report data (i.e., days of use)
  - Compliance with providing biological samples
  - Acceptable rate of protocol deviations/waivers- flexibility vs. data quality

* Monitoring plan- controlling for contingencies

These issues, in addition to the very nature of those afflicted with addiction, present both challenges and opportunities for creative approaches to clinical research.
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THE CONTROL OF HYPERTENSION IN PREGNANCY STUDY (CHIPS) REGIONAL COLLABORATORS’
TELECONFERENCES - AN EFFECTIVE APPROACH TO REGIONAL CO-ORDINATION
Jennifer Menzies¹, Trinh Hoac², Johanna Sanchez², Joanne Kirton¹, Kathryn Mangoff²,
Peter von Dadelszen¹, Sue Ross³, Elizabeth Asztalos², Laura Magee² for the CHIPS Study Group
¹The University of British Columbia, Vancouver, British Columbia, Canada; ²Sunnybrook
Health Sciences Centre, The Centre for Mother, Infant, and Child Research, Toronto,
Ontario, Canada; ³University of Calgary, Calgary, Alberta, Canada.

In large international, multicentre clinical trials, effective communication between the co-ordinating centre and
participating collaborators is vital to the success of the trial. The co-ordinating centre must develop practical
systems to keep collaborators updated on trial progress and protocol, to encourage recruitment and retention,
and to address any potential trial-related difficulties.

The CHIPS Trial (Control of Hypertension In Pregnancy Study) utilises a multitude of tools to communicate with
over 70 participating sites in 13 countries, including weekly recruitment updates, monthly newsletters, a trial
website, a web-based ‘Research Forum’, and face-to-face collaborators’ meetings. While each of these methods
is effective in distributing trial information to a wide audience, most are either expensive, or only allow for a one-
way exchange of information with limited/no opportunity for dialogue. Also, there are often trial-related issues
that are not common to all participating centres, but rather are country or region-specific.

In an effort to address these shortfalls in common communication methods, the CHIPS Trial began hosting
region-specific trial teleconferences in March 2010. These teleconferences have given trial investigators and
co-ordinators the opportunity to discuss regional trial issues in real-time, with their counterparts at other CHIPS
centres in their country (or region), and co-ordinating centre staff in Canada.

We will describe the effectiveness of the CHIPS collaborators’ teleconferences in terms of quantitative (e.g. cost
and time commitments) and qualitative (e.g. descriptive analysis of feedback received from surveyed participat-
ing trial collaborators) comparisons with the other methods of trial communication utilised.

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CLOSE OUT GETS THE ATTENTION: BUT WHO TURNS ON THE LIGHTS?
Fawna Start, Nicole C. Close
EmpiriStat, Inc., Mount Airy, MD, USA

When study personnel are hired or a team is assembled to conduct a clinical trial, there are many aspects related
to conducting those trials that are typically taken for granted. For example, there is the assumption that there
will be co-workers, office supplies, computers, a communication network, and a protocol for the project in which
you were hired to conduct. There are times when a Clinical Program/Network needs to develop the infrastructure
and facilities for conducting research, whether in the US or Internationally, and/or create a centralized outcome
assessment/testing center. Expectations may be that space exists already and an infrastructure established,
whether it is in an independent building or within a hospital setting.

Creating a successful research center, study site for a project, or a centralized outcomes center is paramount
for the Sponsor and their ability to implement and conduct trials, which ultimately determines if any Clinical
Program can succeed. Through the use of two case studies, challenges, benefits and lessons learned through-
out the process are presented. Tips for advance planning will be given, as well as specific examples of where to
start when there is little to start with, and specifics surrounding things you don’t think of like phones, you may
have the equipment but no service, the service you choose may be dependent upon the type of phone you have
or vice versa. Heavy equipment may be required, before it is ordered don’t forget to verify if the structure can
support its weight. The case studies will be summarized with applications to existing Clinical Trial Programs and
programmatic considerations.
QUALITY, QUANTITY AND INFERENCE: WHAT CAN WE LEARN FROM HOSPITALIZATION ENDPOINTS?

Liz Thomas, April Slee
Axio Research, LLC, Seattle, WA, USA

Background: Composite outcomes including hospitalization have gained popularity in recent cardiovascular (CV) trials. The clinical utility of these outcomes are widely debated. Objective: To explore rates, regional differences and relationship with death of hospitalization for any cause (Any Hospitalization), CV hospitalization (CVH) and ICU hospitalization (ICUH). Methods: We calculated rates for Any Hospitalization, CVH and ICUH in AFFIRM. We used proportional hazards with time-varying covariates to determine whether events were associated with increased risk of death. We also examined differences in the effects of treatment and region across outcomes. Results: Patients were 3.9 times more likely to be hospitalized, 2.8 times more likely to have a CVH and 1.4 times more likely to have an ICUH than to die during the study. There was a 12.8-fold increase in the risk of death after Any Hospitalization, a 3.3-fold increase after CVH and a 6.2-fold increase after ICUH, adjusted for treatment (p<.0001 for each comparison). The relationships between Hosp, CVH, ICUH and death were consistent across geographic region. However, there were significant treatment differences in Any Hospitalization (HR=1.2 for rhythm versus rate, p<0.001) and CVH (HR=1.4, p<0.001), whereas ICUH (HR=1.1, p=0.195) and the primary outcome of death (HR=1.14, p=0.083) showed only a trend toward significance. Conclusions: 1. Hosp, CVH and ICUH had increased event rates compared to death, and were strong predictors of death. Any Hospitalization was the most frequent of these outcomes, and surprisingly, was associated with a higher increase in risk of death than CVH or ICUH. 2. There was no evidence of regional differences in the clinical severity of hospitalization outcomes.

INCORPORATION OF AN ADDITIONAL INTERIM ANALYSIS DURING THE RUNNING OF A RANDOMISED CLINICAL TRIAL USING GROUP SEQUENTIAL DESIGN METHODOLOGY

Helen Marshall¹, Rob Coleman², Richard Bell³, David Cameron⁴, David Dodwell¹, Matt Seymour¹, Roger A’Hern⁵, Michelle Collinson¹, John Whitehead⁶, Walter Gregory¹

¹Leeds, West Yorkshire, UK; ²Sheffield, South Yorkshire, UK; ³Geelong, Victoria, Australia; ⁴Edinburgh, Scotland, UK; ⁵Sutton, Surrey, UK; ⁶Lancaster, Lancashire, UK

AZURE is a multi-centre, randomised trial investigating adjuvant zoledronic acid in 3360 breast cancer patients; disease-free survival (DFS) is the primary endpoint. The trial design incorporated one interim analysis to assess for efficacy when at least half the number of DFS events had occurred. This was carried out in 2008 at a stringent alpha level (two-sided 0.005) to retain an overall two-sided 5% significance level using O’Brien and Fleming’s (1979) alpha spending function; the outcome was no data release. Due to a considerably lower than expected DFS event rate, final analysis is now estimated to occur in 2012; however clinical practice has clearly started to change in the absence of confirmatory evidence. The Trial Steering Committee therefore felt a change in the analysis plan was desirable to inform current and future clinical practice in a timely way.

To preserve study integrity and to retain the overall alpha level, it was agreed to conduct an additional interim analysis when at least 75% of the number of DFS events had occurred and to include stopping rules for both efficacy and ‘lack of benefit’ that were seen to be clinically meaningful; these were developed with an independent statistician not having access to the first interim analysis result. Probabilities of declaring a false-positive and false-negative result at the second interim analysis were chosen to be 0.5% (one-sided) and 5% respectively. Using group sequential design methodology (Whitehead, 2010), this corresponded to DFS hazard ratio (HR) stopping boundaries of 0.83 and 0.94: declare efficacy if HR<0.83, declare ‘lack of benefit’ if HR>0.94 or no data release if HR = (0.83, 0.94).

Changes to an analysis plan may be required during the running of a trial. Incorporation of an additional interim analysis using group sequential design methodology is an appropriate solution.
THE CHALLENGES OF RECRUITING FOR AN ANCILLARY STUDY INITIATED AFTER AN ONGOING CLINICAL TRIAL

Letitia H. Perdue1, Walter T. Ambrosius1, Emily Y. Chew2, Ronald P. Danis3

1Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, NC, USA; 2Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, MD, USA; 3Fundus Photograph Reading Center, Department of Ophthalmology, University of Wisconsin, Madison, WI, USA

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) is a clinical trial determining the effects of tight control of glycemia, blood pressure, and management of dyslipidemia in type 2 diabetics. Diabetic retinopathy, a major microvascular complication, was added as a primary outcome for the main ACCORD trial. The ancillary eye study began recruitment almost a year after recruitment for the main trial began.

The barriers to timely and successful recruitment of participants in an “ancillary” study are addressed. The major barriers to recruitment of persons with diabetes into an “ancillary” or “optional” is early planning, recruitment and inclusion of all study team members, and ensuring team members can describe the study and benefits to the participants.

The certification of the ophthalmic clinics required good communications between the clinical sites, the coordinating center, and the fundus reading center. Identifying qualified and willing eye clinics presented a challenge in several locations. Ophthalmology offices were often patient-care based rather than academic and often not experienced in clinical research and the requirements that entails. The participating ophthalmologists/optometrists must have sufficient knowledge of the main trial as well as the eye study to be effective members of the research team.

Participants, investigators, and the clinical coordinators may have the perception that opting out of this important outcome is a choice. Clinics that presented this ancillary study as an integral part of the main trial were able to achieve high recruitment rates.

In the development of studies of an important outcome measurement, it is important to set realistic timelines for site, and patient, recruitment in order to ensure success of the study. Incorporating ancillary studies at baseline is optimal. However, when this is not possible, it is important to educate all study personnel regarding the importance as part of the entire study from the beginning.

RESOLVE PROBLEMS AND ERRORS - CORRECTIVE AND PREVENTIVE ACTIONS (CAPA) FOR CLINICAL TRIALS

Jochen Dress, Christine Georgias, Heike Mönkemann, Ursula Paulus

Clinical Trial Center Cologne (BMBF Grant 01KN0706), Cologne, Germany

To ensure quality in clinical trials, patient safety, and data validity, continuous improvement is essential. We have to spot, correct, and avoid problems and errors under changing conditions, adapting and learning continuously. CAPA is required for medical device trials by regulatory authorities. It has started to propagate into the GCP domain [1], [2]. CAPA allows to handle problems and errors systematically. CAPA ensures that causes are analyzed and appropriate corrective and preventive measures are devised and put in action. Establishing CAPA requires a culture of trust. It can hurt to analyze the cause of a problem or error. Yet, if we turn a blind eye to problems and errors, we risk patient safety and trial validity. Finally it will turn out to be expensive. With CAPA we can handle problems and errors efficiently and effectively. We introduce a CAPA process that is designed to capture problems and errors comprehensively and to concentrate on those that are relevant. Our first CAPA theme was the introduction of a process for the management and accountability of Investigational Medicinal Products (IMPs) in clinical trials sponsored by the University of Cologne. We use a variation of the A3 form of Toyota [3] to structure and document a CAPA theme. We evaluated different D8-Reports (e.g. [4], [5]) and found them too complex. We looked for an easy and scalable access to CAPA management. In our considerations regarding the design of the CAPA process, it was important for us to treat resources with care, to stay flexible, and to improve learning by implementing appropriate feedback loops. Our report will deal with the following questions: * Why should we care about CAPA? * How can we proceed? * How can we identify the relevant CAPA themes?
IMPLEMENTING MULTIPLE BP MEASUREMENT METHODS IN AN RCT: THE BLOOD PRESSURE IN HEMO DIALYSIS (BID) PILOT STUDY

Jennifer Gassman, Dana Miskulin, Karen Brittain, Susan Paine, Andrew Levey, Ajay Singh, Michael Rocco, Phil Zager

Cleveland Clinic, Cleveland, OH, USA

The Blood pressure In Hemo dialysis (BID) Pilot Study is funded by NIH/NIDDK and Dialysis Clinic, Inc. (DCI), a not-for-profit provider. The Cleveland Clinic Data Coordinating Center (DCC) recently implemented training, certification, and longitudinal data collection for Standardized Blood Pressure (StBP) in the AASK Trial (JAMA2002-288(19):2421-31), Ambulatory Blood Pressure (ABPM) in the AASK Cohort Study (ArchInternMed2008-168(8):832-9), Home Blood Pressure in the FHN Nocturnal Trial (KI2007(71),349-359), and Dialyzer Blood Pressure in the FHN Daily Trial (NEJMonline11202010). The BID Pilot Study starts in early 2011 and utilizes all four methods.

Design issues include frequency of measurement, forms development, data collection and transmission, and training for patients and StBP measurers.

Use of ABPM machine output without a specialized processing center will require multi-step data transmission, with each site’s data first transmitted to the DCI Clinical Coordinating Center (Zager, New Mexico) for processing and subsequent transmission to the DCC for management, QC, and analysis.

Little has been documented on acceptability of Home Blood Pressure in hemodialysis patients, who spend three days/week dialyzing and may require special encouragement for BP measurement/data collection on non-dialysis days. Challenges with frequency of measurement in the FHN Nocturnal Study led to fewer required measurements per patient year in BID. Likewise, ABPM has seldom been used in hemodialysis patients. Special encouragement may be required.

StBP measurements are often used in clinical settings, but the BID pilot study will be the first to document standardized measurement (requiring time and serenity) in the setting of a bustling dialysis unit.

In addition to testing the appropriate implementation and safety of randomizing hemodialysis patients to two levels of BP control, the BID pilot study will provide clinical BP level data and patient protocol adherence data to determine which BP measures will be utilized in the subsequent BID full scale randomized clinical trial.

MULTI-SITE CLINICAL TRIALS PROTOCOL AND DATA MANAGEMENT TRAINING: OVERCOMING CHALLENGES IN THE AGE OF TECHNOLOGICAL DISTRACTION

Suzanne E. Gillespie, Reesa Laws, Alan Bauck, Kim Funkhouser

Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA

Our society has become increasingly distracted and consumed by technology. In recent years our clinical trial staff trainees have gone from a group largely intimidated by computers and technology to one who cannot live without their smart phones and constant e-mail access. Preparing hands-on trainings for clinical trials protocols and data management requires careful planning with the expectations of the increasingly tech savvy audience in mind. This presentation will detail challenges at the planning, implementation and follow-up stages of a training and discuss approaches and methods for overcoming them.

During the planning stage of the training one must not only make sure that all the logistics are in place before the training, but it is also crucial to consider how to engage the trainees and ensure that they will be absorbing and retaining the necessary information. During the implementation of the training you should expect the unexpected. For example, technically savvy trainees may move ahead in the training and trigger unexpected results in the system or interpret material incorrectly. There may also be great variation of both research and technical experience among the trainees, which can make the training take much longer than anticipated. There is also the challenge of keeping your distracted trainees engaged, which often means setting clear expectations about the use of technology during the training. Finally, it is important to plan for follow-up training. Examples of this may include having a check-in call or a pre-initiation site visit, or it may be a plan for re-certification on an annual or semi-annual basis.
Protocol trainings are complex and time consuming for both the trainers and trainees. In order to utilize the time spent effectively for all it is essential to prepare for protocol trainings with your audience’s requirements, limitations, and experience in mind.

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**ORDCRM: AN R PACKAGE FOR VARIATIONS OF THE LIKELIHOOD-BASED CONTINUAL REASSESSMENT METHOD DESIGN FOR DOSE FINDING CLINICAL TRIALS WITH ORDINAL TOXICITY GRADING**

Emily Van Meter, Elizabeth Garrett-Mayer, Dipankar Bandyopadhyay, Heidi Weiss

*Markey Cancer Center – University of Kentucky, Lexington, KY, USA*

We introduce the R package, ordcrm, which provides the necessary functions for implementation of dose finding clinical trial design variations of the likelihood-based continual reassessment method (CRM). This package specifically incorporates three different dose finding designs: the proportional odds model CRM and continuation ratio (CR) CRM for ordinal toxicity grades as specified by Common Toxicity Criteria (CTCAEv3.0) and the original binary likelihood-based CRM, which dichotomizes toxicity outcomes based on pre-specified dose-limiting toxicity (DLT) criteria. For each of these three dose finding designs, there are functions to create the pseudodata necessary to build the starting models and obtain the first dose to test in patients for a trial given a desired DLT rate. There are also functions to re-estimate the next dose to test in patients given the original pseudodata and current collected patient toxicity outcomes accrued in the trial. This package also provides functions to run simulations for these three designs to assess design performance under various scenarios. All functions give clinical investigators and biostatisticians the flexibility to specify target DLT rates, cohort sizes, overall sample sizes, safety constraints, and continuous or discrete dose levels in the dose finding design. We also allow the option to combine toxicity grades 0 and 1 into one category should clinical investigators wish to do so. This R package provides the necessary functions for biostatisticians to easily implement these ordinal likelihood-based CRM designs during phase I trial development, while also providing clinical investigators a clear description of the trial study design. We provide an example of how this R package could be utilized in a phase I trial currently under development at the University of Kentucky Markey Cancer Center.

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**A MULTIFACETED APPROACH TO THE QUERY PROCESS**

Trinh Hoac¹, Jennifer Menzies², Johanna Sanchez¹, Laura Magee², Elizabeth Asztalos¹, Kathryn Mangoff¹, Joanne Kirton², Sue Ross³, and Peter von Dadelszen² for the CHIPS Study Group

¹Sunnybrook Research Institute, The Centre for Mother, Infant, and Child Research, Toronto, Ontario, Canada; ²The University of British Columbia, Vancouver, British Columbia, Canada; ³University of Calgary, Calgary, Alberta, Canada

The Control of Hypertension In Pregnancy Study (CHIPS) is an international multicentre randomised controlled trial with over 70 participating centres in 13 countries and a recruitment goal of 1028 patients. The CHIPS Data Co-ordinating Centre (DCC) continuously educates and monitors participating research centres to ensure Case Report Forms (CRFs) are accurately completed. The CHIPS DCC handles, on average, 2,250 CRFs per year.

Complete and accurate data on the CRFs are important for the overall integrity of a study and thus requires automated and effective early detection processes. The CHIPS DCC implemented an automated query process using SAS® software and a Microsoft® Access database to capture incomplete answers, validate data and eliminate inconsistencies across forms. Additionally, various approaches are used to educate users: a web discussion forum, self taught Microsoft® Powerpoint presentations, and monthly newsletters highlighting common queries. These various approaches are expected to increase the number of accurately completed CRFs, and reduce the volume of queries generated.

The multifaceted approach to the query process in the CHIPS Trial was implemented to ensure data quality control.
Not all applicants who present an impressive clinical background and ‘interview well’ for a postpartum depression treatment trial that trains nurses in interpersonal psychotherapy (IPT) will demonstrate ‘IPT-trainability’. Recruiting seemingly well-suited applicants who end up performing poorly is time-consuming and costly. Therefore, the trial’s interviewing process evolved to incorporate both in-person interviews and the use of standardized patients (SPs) to better assess applicants’ trainability and potential as effective IPT Trial Nurses. Selected applicants participate in a simulated, telephone-based session with a ‘new mother’ diagnosed with postpartum depression (SP/actor). The SP is provided background information about her character, and the applicant plays the role of ‘IPT Nurse’ getting to know the ‘new mother’. The trial coordinator remains on the telephone with both parties during the simulated session. Following the session, the applicant hangs up the telephone so that the SP can privately provide feedback. The trial coordinator then calls the applicant to discuss her own reflections about her performance; this is done to assess the applicant’s receptiveness to criticism and how she might approach actual IPT training/supervision if chosen to work in the trial. The entire mock session and follow-up discussions are digitally audio-taped so that supervisors can listen and comprehensively evaluate the applicant’s basic therapeutic skills and traits (e.g., insight, empathy, warmth, approachability). Those who exhibit such attributes are offered an IPT Nurse position. Several nurses experienced the simulated sessions and are currently progressing in the final phase of IPT-training. In conclusion, the use of SP mock sessions have helped to provide a clearer sense of an applicant’s therapeutic potential and enhanced the efficiency of the hiring/training process of IPT Nurses.

Many clinical trials use estimated glomerular filtration rate (eGFR) to study patients with chronic kidney disease (CKD). Like many other laboratory measurements, eGFR is very variable, so that trials typically use several measures of eGFR to define entry criteria, baseline measurements, and outcomes. For example, trials with inclusion criteria defined in terms of screening eGFR often calculate the screening value as the average of two or more measurements. Some trials also define baseline eGFR as a weighted average of the screening and a single post-screening, pre-treatment measurement. Both efficacy and safety outcomes typically use change from baseline eGFR (either as a continuous measure or a categorical variable) because clinicians say they find change meaningful.

Statistical analysis of change from baseline has well-known pitfalls. If the calculation of baseline eGFR includes screening measurements on which entry into the trial is dependent, regression towards the mean can occur. There are different definitions of change commonly used in analyzing eGFR, including change in CKD stage, percent change, and absolute change. Even if the same baseline and post-baseline measurements are incorporated into calculating change, conclusions drawn from analysis of change using one definition may differ from analysis using another definition. Further, the calculation of baseline (e.g., single vs. averaged measurement) impacts the results.

This presentation uses eGFR data from a randomized clinical trial to illustrate how various definitions of baseline and change can influence the results.
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CHALLENGES OF REPORTING AND CODING ADVERSE EVENTS IN CLINICAL TRIALS

Hua Carroll

KAI Research, Inc. Rockville, MD, USA

To create a safety profile for an investigational drug, adverse event (AE) information is collected and analyzed throughout the cycle of clinical trials. AEs are coded with standardized medical terminology prior to being analyzed. Collection of clean AE data facilitates AE coding and reduces query time.

This presentation discusses the challenges in adverse event reporting and coding in clinical trials and presents our best practices in overcoming these challenges:

- Need for adverse event coding using MedDRA
  - To facilitate a standardized and medically meaningful safety data presentation
  - To facilitate easy retrieval and effective reporting of drug safety information for analysis and regulatory compliance

- Challenges in adverse event reporting
  - Recognize all reportable AEs
  - Common mistakes in reporting AEs
  - AE reporting in special situations

- Approaches to adverse event coding
  - Training
  - Site vs. centralized AE coding
  - Medical review
  - MedDRA version upgrade during clinical trials
  - Analysis of MedDRA MSSO recommendations
  - MedDRA upversioning technology

The reporting and coding of adverse events is a dynamic process which, when handled properly, will increase the efficiency and credibility of clinical trials.

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SYSTEMATIC REVIEW OF THE METHODS AND EFFECTS OF SOURCE DATA VERIFICATION IN CLINICAL RESEARCH

Roxanne Ward/Dean Fergusson

Children’s Hospital of Eastern Ontario Clinical Research Unit, Ottawa, Ontario, Canada; The Ottawa Hospital Research Institute Clinical Epidemiology Program, Methods Centre, Ottawa, Ontario, Canada

Background: Good Clinical Practice (GCP) Guidelines were established in 1996 and describes the responsibilities of all participants in the conduct of a clinical trial. These guidelines state that clinical trials should be adequately monitored to ensure that the data are complete, accurate and verifiable. Source data verification is conducted as part of monitoring to compare data collected at the source to that which is recorded on a case report form and is the only method to guarantee that data are complete, accurate and verifiable. However, GCP Guidelines are vague and lack evidence as to the degree of source data verification required and whether or not source data verification affects study outcomes. Objectives: The primary objective of this systematic review is to establish the evidence base for source data verification; specifically to examine published methods of source data verification and examine the effect of source data verification on study outcomes. Methods: Using an explicit search strategy we searched Pubmed, EMBASE and The Cochrane Library for all studies, guidelines and reports where a method of source data verification was documented and evaluated or that reported on the effect of source data verification on study outcomes (including non-English articles). Two content experts independently conducted the initial screening; consensus was achieved, followed by subsequent reviews. Hand searching of titles will be conducted in relevant journals in addition to reference lists of relevant studies, web sites of clinical trial associations, research groups, and conference proceedings of clinical trial organizations. Results: There were 653 articles for the initial screening. Subsequently, 73 were included; 10 were comparative or clinical studies, and the remaining were reviews or reports. Significance: We will synthesize the evidence from the search strategy and hand searching to identify methods of source data verification and reported impact on study outcomes.
IMPROVING CLINICAL TRIAL DATA COLLECTION: A WEB-BASED SYSTEM TO DYNAMICALLY GENERATE STUDY FORMS WITH INTEGRATED BARCODES

Darrin Harris, Mark D. King, Jason Griffin, Scott Rushing, Gregory N. Evans, David Reboussin
Wake Forest University School of Medicine Winston-Salem, NC, USA

The Systolic Blood Pressure Intervention Trial (SPRINT) is a 2-arm, multi-center, randomized controlled trial designed to test whether a treatment program aimed at reducing systolic blood pressure well below current guidelines will reduce cardiovascular disease risk. About 9250 participants will be recruited and followed for 4-6 years at approximately 90 clinics nested within 5 clinical center networks across the continental United States and Puerto Rico. As the SPRINT Central Coordinating Center, our objectives in designing a web-based data collection system included the efficient collection of high quality data with minimal staff burden. SPRINT data is recorded on paper forms during participant visits and then subsequently entered into a ColdFusion/SQL Server web-based data management system. To facilitate data collection, the Coordinating Center developed an application within the system that dynamically generates PDF versions of study forms which are then printed and used by the clinical staff. This allows for: 1) forms to be pre-filled with participant identifiers and data from previous visits, 2) more efficient management of form changes, and 3) a flexible system for printing forms in different languages. Forms are generated dynamically as they are printed, and include a barcode identifier to associate the paper form with a specific participant and visit. This alleviates the need for clinical staff to write participant identifiers on forms or use peel-off labels. When the barcode is scanned, the user is taken directly to the data entry screen for that form, that participant and that visit without typing or selecting any participant IDs or visit codes. Using this method to print forms and to collect and enter data, not only reduces the workload of clinic staff, but also helps prevent data entry errors. The poster will describe the system in detail discussing the benefits and challenges.

A CENTER PERFORMANCE ASSESSMENT TOOL IN A MULTICENTER CLINICAL TRIALS NETWORK

Elizabeth Thom
Eunice Kennedy Shriver NICHD MFMU Network, Bethesda, MD, USA

Background: The NICHD MFMU Network, currently consisting of 14 clinical centers and a data coordinating center (DCC), has conducted obstetrical trials and observational studies since 1986. The centers re-compete to participate every 5 years. In 2000, the NICHD asked the DCC to provide a report summarizing each center’s performance on multiple studies (report card) as an aid to the review of centers’ applications. Since 2000, the report card has been refined and used by the Network to identify areas for improvement. Report cards were also used for grant application review in 2005 and 2010.

Methods: Performance is divided into two main categories: recruitment/retention and adherence/quality. Recruitment/retention is described for each center by the average percent of patients contributed over all studies conducted; and by the average percent of patients with complete follow-up data. The centers are ranked on recruitment and retention separately, and the sum used to create the overall rank. For adherence/quality, four measures are used: protocol adherence (the average rate of protocol violations per enrolled patient), data quality (the average rate of edit checks per patient), data timeliness (the percent of forms entered late), and timeliness of study start-up (time of starting after the first center start date). The centers are ranked on each of the four measures and the sum used to create the overall rank for adherence/quality. The report card is updated regularly: each center can compare its performance in each category with the other centers to identify areas for potential improvement. A cumulative version reflects each center’s performance for the preceding 5-year period.

Conclusion: This one-page summary is a succinct and useful tool for comparing center performance, and has been used to pinpoint progress and areas of concern. Grant review committees are provided with objective data for comparison of center performance.
ENROLLMENT AND COMPLIANCE IN A NATIONAL PHYSICAL ACTIVITY STUDY: AN INTERIM REPORT FROM THE REASONS FOR GEOGRAPHIC AND RACIAL DIFFERENCES IN STROKE (REGARDS) STUDY

Virginia J. Howard, J. David Rhodes, Anh Le, Natalie Colabianchi, John E. Vena, Veena Seshadri, Margaret S. Stewart, Steven P. Hooker

School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA; Arnold School of Public Health, Columbia, SC, USA; College of Public Health, University of Georgia, Athens, GA, USA

BACKGROUND: Innovative clinical trials and epidemiologic studies examining physical activity (PA) now use objective measurement devices (e.g., accelerometers) over self-report. NHANES 2003-2004 accelerometer data were obtained from 74% of participants; 4% were unusable, 26% had 7 days of valid wear, 71% had 4+ valid days. Herein we describe the experience of another national epidemiologic study using accelerometers. METHODS: REGARDS-PA is an ancillary study to REGARDS, a national, population-based, longitudinal study of 30,239 blacks and whites, aged > 45 years, enrolled January 2003-October 2007. Participants are called every 6 months for potential stroke events and starting May 2009, dependent on availability of a device, are asked about willingness to wear an accelerometer for 7 days for REGARDS-PA. Device, instructions, and stamped addressed envelope for return are mailed to consenting participants. Postcard acknowledgement, reminders, and < two calls are made to encourage compliance with wearing device and its return. Participants receive summary results but no financial compensation. RESULTS: By November 1, 2010, 9,502 were asked to participate: 56% consented, 17% deferred, 27% declined. Consent rate for blacks was 35% vs. 66% for whites. Devices were shipped to 5,147 with return rate of 84%; 397 are lost (outstanding > 120 days). Of accelerometers returned/analyzed (n=4016), 81% provided usable data, 4% not worn sufficient amount of time, 15% had incomplete/missing log sheet or device malfunction. Initial inventory of 600 accelerometers was increased to 900. After processing, cleaning, and battery change of returned devices, maximum number of devices ever shipped in a week was 200. A challenge is determining number of days of valid wear. The usual algorithms substantially overestimate non-wear in the REGARDS-PA sample. CONCLUSIONS: While our results compare favorably to NHANES, a limiting factor is availability of accelerometers. Budget and protocol could be re-examined towards consideration of incentives to participate and return devices.

A MODEL FOR CAPITATION PAYMENT IN A MULTICENTER CLINICAL TRIALS NETWORK

Trisha Boekhoudt

Eunice Kennedy Shriver NICHD MFMU Network, Bethesda, MD, USA

Background: The NICHD Maternal Fetal Medicine Units Network, consisting of 14 clinical centers and a data coordinating center (DCC), has conducted obstetrical trials and observational studies since 1986. Until 2008, NICHD funded clinical centers through a base budget which covered limited personnel, and study-specific fixed payments per patient recruited (capitation), which could be used to hire additional staff, and pay for local study expenses (e.g. patient reimbursement, study-specific supplies). In 2008, the DCC took over capitation management through a separate, fixed annual budget.

Methods: To set the capitation rate for a study, the DCC creates a detailed questionnaire for the clinical centers to estimate time spent on patient recruitment (screening, enrollment) and study procedures, and costs of supplies, shipping costs etc. Time is converted into cost by a fixed salary factor. The median estimated cost per patient across all centers is used as the capitation rate. To maintain performance, the capitation payment may be split between study-related events (e.g., recruitment, completion of follow-up, collection of biospecimens, attainment of lab results). The capitation rate may be adjusted, if the estimates are found to be unrealistic. Quarterly cumulative quotas are issued for the number of patients that may be recruited for each study at each center. Factors in setting the quotas include past recruitment, activity in other Network studies, and estimated remaining funds for the current fiscal year. The budget is monitored through a spreadsheet that is updated weekly from the accumulating study data. Quotas are adjusted as the study progresses and are conditional on remaining funds. Centers are paid quarterly.

Conclusion: The DCC has successfully adapted the existing capitation system and has incorporated additional reporting to monitor the budget.
NORMATIVE DATA AND IMPLICATIONS FOR RANDOMISED CONTROLLED TRIALS
Suzanne Breeman, Gareth Jones, Shona Fielding, Seonaidh Cotton
University of Aberdeen, Aberdeen, UK

The 14-item Hospital Anxiety and Depression Scale (HADS) is one example of a patient reported outcome measure that is now extensively used in standard medical practice and health-related research. However, normative data from HADS i.e. data collected from a representative sample of the general population against which all subsequently collected data can be compared, is limited. A recent review revealed only 15 studies that contained data that could be described as ‘normative’ for HADS. These studies were conducted predominately in Europe. The four studies conducted within the UK had limitations, mainly in terms of sample size and/or sample selection.

This scarcity of normative data potentially limits its use as an outcome measure. While this does not impact on the internal comparisons between arms in a randomised controlled trial (RCT), it has implications when considering the impact of an intervention compared to the general population. For example, in RCTs that have used HADS, it may be clinically important to establish if the interventions under investigation impact on anxiety and depression levels compared to those observed in the population. This raises a further issue in terms of the appropriate normative data to compare against. Levels of anxiety and depression vary by gender, age and other social demographic factors and comparisons against normative data that does not represent the population under consideration may lead to false conclusions about the impact of the intervention.

We will report on the use of HADS in RCTs. We will also report approaches to reporting normative data and how this may aid the interpretation of RCTs that have used HADS as an outcome measure.

THE UNIQUE SYSTEM FOR ‘UNNOTIFIED CLINICAL TRIALS TO THE AUTHORITY’ IN JAPAN
Toshinori Murayama, Eriko Sumi, Manabu Minami, Toshiko Ihara, Masayuki Yokode
Translational Reserach Center, Kyoto University Hospital, JAPAN

Besides IND/IDE trials, “unnotified clinical trials to the authority” using unapproved medical technology are allowed in Japan. While the Pharmaceutical Affairs Law does not concern, the Ethical Guidelines, the only regulation for those, were fundamentally revised and enacted in April 2009. Although most of the “unnotified trials” have been conducted only under the permission by the IRB/IEC and institution, The Ministry of Health, Labour and Welfare has established other unique systems for the unnotified trials, i.e., “Senshin-iryo”, Advanced Medical Technology in Japanese, and its subcategory, “Koudo-iryo”, High-level Medical Technology in Japanese. Public health insurance can be exceptionally applied to the trials under these systems for the standard medical practice, other than IND/IDE trials. Since these systems are not based on the full set of GCP/GMP/GLP, the data obtained from the trials under “Senshin-iryo”, or “Koudo-iryo”, are supposed not to be included in Common Technical Documents for New Drug Approval in Japan. The discussion has just begun about these systems and their data utilization in the Central Social Insurance Medical Council. In order to accomplish a variety of trials safely and smoothly, we are developing an educational program to build infrastructure for clinical trials within the Special Research Initiative, named “Strengthening the capacity of project sponsors in academia,” subsidized by the Health Labor Sciences Research Grant. The changing situation will be addressed around Japanese clinical trials in this presentation.
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METHODOLOGY AND CHALLENGES IN EXECUTING A PEDIATRIC CARDIOVASCULAR MULTICENTER RANDOMIZED CLINICAL TRIAL FOR OFF-LABEL DRUG USE.

Victor Zak1, Seema Mital2, Lynn Mahony3, Lynn Sleeper1, Andrew Atz4, Jami Levine5, Piers Barker6, Chitra Ravishankar7, Brian McCrindle2, Richard Williams8, Karen Altmann9, Nancy Ghanayem10, Renee Margossian5, Wendy Chung9, William Border11, Gail Pearson12, Mario Stylianou12, Daphne Hsu13 for the Pediatric Heart Network Investigators

1New England Research Institutes, Watertown, MA, USA; 2Hospital for Sick Children, Toronto, Ontario, Canada; 3University of Texas Southwestern Medical Center, Dallas, TX, USA; 4Medical University of South Carolina, Charleston, SC, USA; 5Children’s Hospital Boston, Boston, MA, USA; 6Duke University Medical Center, Durham, NC, USA; 7Children’s Hospital of Philadelphia, Philadelphia, PA, USA; 8Primary Children’s Medical Center, Salt Lake City, UT, USA; 9Columbia University College of Physicians and Surgeons, New York, NY, USA; 10Children’s Hospital of Wisconsin, Milwaukee, WI; 11Cincinnati Children’s Hospital, Cincinnati, OH, USA; 12National Heart, Lung, and Blood Inst, NIH, Bethesda, MD, USA; 13Children’s Hospital at Montefiore, Bronx, NY, USA

Background: The proven benefit of ACE inhibitor (ACEi) therapy in adult heart failure (HF) has led to widespread off-label pediatric use including HF in complex congenital heart disease such as single ventricle (SV), where children are born with one functioning ventricle. Ventricular dysfunction and growth failure during infancy are common, resulting in empiric ACEi use.

Design: In a NHLBI multicenter, randomized, double-blind trial of the ACEi enalapril versus placebo in infants with SV, subjects were randomized (with stratification and dynamic balancing within center) at <45 days old after first-stage palliative surgery and followed through second-stage surgery to age 14 months. The primary endpoint was weight-for-age Z-score at 14 months. Exclusion criteria included conditions that independently affect growth. Secondary endpoints, obtained prior to planned second-stage surgery and at 14 months, included HF score, BNP, adverse events (AE), and Z-scores for height, head circumference, ventricular mass and volume. Intention-to-treat analysis using longitudinal modeling (with baseline value adjustment) was used to compare growth z-scores.

Results: 230 eligible infants (out of 1245 screened) were randomized at age 20±9 days and 185 completed the trial. Challenges included a low consent rate (43%), subject withdrawal (20%), monitoring drug compliance, need to stop and restart the drug for second-stage surgery, and a high rate of crossovers between treatment arms. Overall incidence of death, transplant and serious AEs did not differ between groups. We observed no benefit of enalapril at 14 months on growth and ventricular function. Pre-specified subgroup analysis also yielded no positive treatment effects.

Conclusions: Challenges of research with fragile SV infants can be overcome. Conservative assumptions in sample size calculation and sharing effective strategies among centers contributed to successful completion of the trial. The trial findings do not support the routine use of enalapril in this population and demonstrate the importance of well-conducted pediatric trials.

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ANALYSIS OF RELATEDNESS TERMINOLOGY FOR ADVERSE EFFECTS IN A PHASE I CLINICAL TRIAL

Marla J. Husnik1, Barbra Richardson1,2

1Fred Hutchinson Cancer Research Center, 2University of Washington

Introduction: The Manual for Expedited Reporting of Adverse Events (AEs) from the Division of AIDS outlines criteria to assess the relationship between AEs and study product use in clinical trials. In the latest Version 2.0, five terms were replaced with two terms, not related and related only. We were interested in how implementation of this new terminology might affect AE analyses in clinical trials.

Methods: We compared AE results by treatment arm for a Phase I clinical trial entitled Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women using combinations of the five relatedness terms as follows:

1. Possibly related, probably not related and not related vs. definitely related and probably related; 2. probably not related and not related vs. definitely related, probably related and possibly related (most equivalent to Version 2.0 definition); and 3. not related vs. definitely related, probably related, possibly related and probably not related.
With generalized estimating equations, we constructed models of definitions 1-3 on study arm accounting for within-participant variation using the exchangeable working correlation structure.

Results: Sixty-one participants reported 172 AEs over a three week period: 3 (1.7%) definitely related, 26 (15.1%) probably related, 58 (33.7%) possibly related, 45 (26.2%) probably not related, and 40 (23.3%) not related. When comparing HEC placebo vs. VivaGel®, the odds ratio (95% confidence interval) for definition 1 was 1.87 (0.53, 6.58) p=0.3, definition 2 was 1.15 (0.45, 2.94) p=0.8, and definition 3 was 2.61 (0.93, 7.35) p=0.07.

Conclusions: We found no statistical significance between arms for definition 2, the relatedness definition most equivalent to Version 2.0. However, results for the coarser or more specific definitions showed a trend toward statistical significance implying that the specificity for interpreting relatedness to product use is important.

P55
A LATENT CLASS MODEL ANALYSIS USING THE MONTE CARLO EM ALGORITHM TO ASSESS ACCURACY OF DIAGNOSTIC TESTS OF CERVICAL NEOPLASIA IN WOMEN WITH ATYPIAL GLANDULAR CELLS OF UNDETERMINED SIGNIFICANCE
Le Kang¹, Randy Carter¹,², Kathleen Darcy², James Kauderer², Shu-Yuan Liao³, William Rodgers⁴, Joan Walker⁵, Eric Stanbridge⁶, Heather Lankes²

¹Department of Biostatistics, University at Buffalo; ²GOG Statistical and Data Center, Roswell Park Cancer Institute; ³Department of Pathology, St. Joseph Hospital; ⁴Department of Pathology, Lenox Hill Hospital; ⁵Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center; ⁶Department of Microbiology and Molecular Genetics, University of California at Irvine

Objective: Compare diagnostic accuracy of biomarker-based tests with that of an imperfect ‘gold standard’ (‘GS’) for diagnosing significant cervical lesions (SCL) in women with a cytological diagnosis of atypical glandular cells of undetermined significance (AGC) in the absence of true disease status.

Methods: Latent class modeling methods were extended and applied to assess diagnostic accuracy of CA-IX; high-risk human papillomavirus (HPV), assessed by Hybrid Capture II (HPV-HC2); and of an imperfect histology-based ‘GS’ assessment. The Monte Carlo EM algorithm was employed to estimate diagnostic accuracy parameters for each test and the age-specific prevalence of SCL. The missing information principle and the bootstrap method were employed to obtain the standard error estimates. An optimal diagnostic rule based on CA-IX and HPV-HC2 in combination was derived.

Results: The ‘GS’ was nearly perfect but required an invasive procedure and pathologist review. CA-IX had the lowest sensitivity. HPV-HC2 had a high sensitivity (99.92%) and low false negative rate (0.01%) but had marginal specificity (87.75%) and an unacceptably high false positive rate (>16.22%). Combining CA-IX and HPV-HC2 did not improve diagnostic accuracy. The age-specific prevalence of SCL was consistent with previously observed trends in HPV infection.

Conclusions: A negative HPV-HC2 result is sufficient to safely rule out SCL and forego the invasive treatment that is often provided to women from the US with AGC. Such treatment is not safely indicated by a positive HPV-HC2 result, as at least 16.22% of women with a positive HPV-HC2 result did not have SCL and underwent an invasive procedure that was not necessary. Further research to find additional biomarkers that will increase specificity and allow identification of HPV-HC2 positive women who have SCL is needed.
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META-ANALYSIS OF CARDIAC SURGICAL TRIALS CONCERNING INTRAMYOCARDIAL BONE MARROW STEM CELL TRANSPLANTATION
Aenne Glass; Peter Donndorf; Alexander Kaminski; Gustav Steinhoff; Guenther Kundt

Institute for Biostatistics and Informatics in Medicine and Ageing Research, University of Rostock, Rostock, Germany; Department of Cardiac Surgery, University of Rostock, Rostock, Germany

Objectives: Clinical studies have suggested that intramyocardial bone marrow stem cell (BMSC) transplantation combined with coronary artery bypass surgery (CABG) might improve left ventricular function, and thus prove to be a new therapeutic option for patients with endstage ischemic heart disease. To quantify the overall treatment effect of three functional parameters we conducted a meta-analysis of relevant studies, regarding efficacy and safety of BMSC transplantation during CABG. Methods: Database searches (PUBMED, MEDLINE, Cochrane trials register, ClinicalTrials.gov) revealed 4 RCT’s and 2 cohort studies to include. The analysis (STATA 9.0) was stratified by the difference between BMSC and control group. Each mean difference was weighted by the inverse of variance, before being pooled with either the fixed or random effects model, depending on I-squared and Cochran’s Chi-square-test of homogeneity. In case of heterogeneity a meta-regression analysis was added. To test significance of the overall effect we performed the z-test. The presence of publication bias was assessed by funnel plots, Begg’s rank correlation test and Egger’s weighted regression method. Results: Compared with control group, the BMSC group showed significant improvement of the left ventricular ejection fraction from baseline (5.40%, 95%CI: 1.36 to 9.44, p=0.009), and improvement of overall change of left ventricular end-diastolic volume (9.55 ml, 95%CI: -2.82 to 21.92, p=0.13). Major adverse cardiovascular events were not significantly different. Conclusions: BMSC transplantation in combination with CABG is associated with improvements of functional parameters in patients with chronic ischemic heart disease. Surgical intramyocardial BMSC transplantation appears to be safe.

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DETERMINING THE OPTIMAL BIOMARKER CUTOFF FOR DEFINING A SUBPOPULATION OF CANCER PATIENTS WHO MAY BENEFIT FROM TREATMENT
Don (Dongguang) Li, Tao Wang, Stephanie Green

Pfizer Inc., New London, CT, USA

The recent rapid development in biologic knowledge brings new hope to cancer treatment. Objectively measured biomarkers have been showing promise in refining cancer diagnosis and in identifying the right treatment for the right patient. Cancer biomarkers are categorized into prognostic and predictive types. Predictive biomarkers are measured before treatment to identify the patients who will or will not benefit from a particular treatment. This idea opened a new era of cancer clinical trials - seeking targeted (or personalized) treatment. Nowadays, seeking biomarker determined target subpopulations has become a common practice in cancer clinical trials.

There are various exploratory methods used to identify patient subsets with more sensitive response to a specific treatment using a potential biomarker. One common approach is to identify a optimal cutoff on the biomarker scale at which the most obvious difference in treatment effects between the high and low subsets is apparent. Such difference can be measured in a number of ways, including magnitude or significance of hazard ratios or interaction terms and area under ROC curve. Working with biomarker data in the past two years to identify the sensitive patient subset with respect to time-to-event endpoints, our team has developed statistical methods and algorithm to automatically explore cuts of continuous biomarkers by comparing the treatment effects between the high and low patient subsets. A SAS macro program that automates the process of examining various cuts, conducting the analysis, and generating the summary reports and plots is provided. A simulated dataset was used to demonstrate the statistical method and SAS macro. The method was also implemented to real data.

This program could be useful as the first step in screening for potential predictive markers in cancer trials. The findings may trigger further validation and provide hypotheses for more efficient trial design using targeted subpopulation.
IMPLEMENTATION OF COGNITIVE SCREENING AND CONFIDENTIALITY ASSURANCE WITH AN ON-LINE SURVEY FOR MEASURING POPULATION PREFERENCES

Colleen M. Peters, Dustin L. Stwalley, Steven M. Kymes

Washington University School of Medicine, St. Louis, MO, USA; Center for Economic Evaluation in Medicine, St. Louis, MO, USA

Background: We constructed a web-based interview to elicit utilities from a community based sample. Per Institutional Review Board (IRB) guidelines, survey responses could not be linked to a specific person. Research shows that people are more likely to participate in a study when provided with an incentive, so we planned to provide a $10 gift card but needed to acquire name and address without linking to a specific survey response. In addition, we needed to create a cognitive screening tool to provide an objective measure for disallowing selected respondents. Methods: The survey was password protected to deter unauthorized access, and we address IRB concerns regarding respondent confidentiality by assigning each unique password five times to different screened volunteers. Once they completed the utility survey, respondents registered their name and mailing address to receive a gift card on a second survey that was linked from the first survey. For cognitive screening, we used the page from the survey that gave an example of a discrete choice experiment as part of the instructions. One choice consisted of all positives, the other choice was all negatives the incorrect choice. If someone answered incorrectly, the instruction page appeared again and respondents had a second chance to answer correctly. 1,579 people were recruited via email; 753 passwords given out; 519 survey responses acquired. Results: We increased the original study target of 150 responses to 400 qualified responses and completed the recruitment within 10 weeks. 2% of the surveys were not completed and 20% were disqualified for failing the cognitive screening or answering the instruction test page incorrectly two times. Conclusion: It is possible to address issues of cognitive screening as well as respondent confidentiality and still provide a stipend for participants in a web-based survey.

AN EFFICIENT WEB-BASED APPROACH TO MANAGING A COMPLEX CAUSE OF DEATH REVIEW PROCESS

Jennifer Rosenbaum1, Pamela M. Marcus2, Brenda Brewer1, Ramachandra Chanapatna1, Kathy Clingan1, Kristen Keating1, Alan Morgan1, Nancy Payte1

1Westat, Rockville, MD; 2National Cancer Institute, Bethesda, MD, USA

The National Lung Screening Trial (NLST) is a randomized controlled trial designed to determine whether screening with low-dose helical computed tomography reduces lung cancer mortality relative to screening with conventional chest x-ray in persons at elevated risk of lung cancer. The NLST Endpoint Verification Process (EVP) assigns participant causes of death in order to minimize error inherent in using death certificates alone. The goal of the EVP is to ascertain whether deaths are due to lung cancer, complications of diagnostic evaluation or treatment for lung cancer, or other causes.

In support of EVP activities, one Coordinating Center (CC) developed the Endpoint Verification Internal Computerized Tracking System (EVICT), a versatile Web-based tracking and data management tool. EVICT supports the activities of 33 study sites, two CCs, and five members of the Endpoint Verification Team (EVT). The work flow begins when the CC Data Manager receipts death certificates into EVICT, proceeds through the selection and review processes, and ends with the EVT’s final decision on the cause of death for those selected for review.

The implementation of EVICT has improved the efficiency of the EVP. The system supports various user roles and produces multiple reports necessary to facilitate and monitor the process. EVICT can be customized to create a comprehensive and integrated system that can be utilized by other studies that require management and review of death certificate data. This presentation will give an overview of the capabilities and value of EVICT, as well as the lessons learned from the development of this efficient tool.
Certification of clinical center staff and facilities when there are a high number of roles, high number of centers and satellite sites with shared personnel, several working groups (e.g. coordinating center, reading centers) with certifiers responsible for review of submitted materials, and a wide variety of tasks required for certification is challenging. The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) developed a web-based, interactive certification system that provided real time information to staff at Clinical Centers and certifiers about the status of certification requirements for staff and sites. Applicants viewed role-specific checklists displaying outstanding items, dates of successful completion, and contact the information for the certifier. Links to other databases (e.g., central testing service for visual acuity examiners, study-wide contact information system) allowed efficient transfer of information without duplicating requests to clinical center staff. The system allowed interactive completion of role-specific knowledge assessments, with immediate grading, provision of the appropriate section of the protocol for incorrect responses, and updating of the status if the test was passed. Certifiers reviewed submitted materials such as photographic images, completed data collection forms, and documentation of passing patient oriented research courses and updated the completion status and/or provided feedback to each applicant. The system automatically generated notices to certifiers when action was needed. The system was a user friendly, flexible tool that allowed users to add and delete study roles as required. A separate component tracked the progress of clinic certification by maintaining a summary of certifications for required roles and documentation of specific equipment and approvals. This system has certified 1176 staff in ten roles and feedback from all users has been uniformly positive.

The National Lung Screening Trial (NLST) is a randomized controlled trial designed to determine whether screening with low-dose helical computed tomography reduces lung cancer mortality relative to screening with conventional chest x-ray in persons at elevated risk of lung cancer. The NLST involves investigators from 33 sites across the US and has generated a robust data set that will be available for secondary analyses and ancillary research. NLST research subcommittees provide a forum for the exchange of ideas for all of the trialists and foster the development of ancillary studies, manuscripts, and presentations on behalf of the trial. To maximize productivity, the Coordinating Center (CC) provides a support team composed of a CC Lead and the Data QA Manager for each subcommittee, as well as one Review Process Coordinator that supports all subcommittees. The team offers guidance to subcommittee members for proposal development and submission; reviews proposals and data requests; assists with data interpretation; and liaises with reviewers, investigators, and the Data and Safety Monitoring Board. Responding to client needs, the CC developed policies and procedures related to subcommittee activities and information sharing. This presentation will explore our approach to fostering a collegial and productive subcommittee environment. It will describe the structure and dynamics of the support team and the interactive process for developing subcommittee guidelines to maximize the impact of NLST research within the scientific community.
AUTOMATED DRUG ORDERING IN A COOPERATIVE GROUP SETTING
William E. Elgie, Quang Le, Suzanne Baskerville, Mark Brady
GOG Statistical & Data Center, Buffalo, NY, USA

The GOG Statistical and Data Center (SDC) has developed a secure, automated, web-based system to facilitate drug ordering/reordering for GOG protocols where protocol directed therapy drug requires the authorization and distribution from the National Cancer Institute’s (NCI) Pharmaceutical Management Branch (PMB). The process utilizes the SDC’s electronic data entry system (SEDES) and web-based patient registration system (REGWEB). The process begins with a patient registration to a GOG protocol via REGWEB, which automatically sends an email to the PMB, alerting their staff. The patient’s Calendar of Expected Events/Forms within SEDES is updated to include a Drug Order/Reorder (DORA) form for the clinical staff to complete. Information on the form is preloaded where possible, such as the treating physician’s CTEP Investigator ID, in order to assist the clinical staff. For each submission, a transaction is logged, and a transaction receipt is provided for the clinic’s records. Each evening a nightly process securely and automatically transfers all new drug orders/reorders to the PMB. The PMB’s electronic inventory system is updated and schedules shipment of the study agents to the treating physician. For subsequent study drug reorders, the clinical staffs use SEDES to submit orders according to the patient calendar. Reorder forms are also prefilled except for data that may have changed, such as the patient’s weight. This drug ordering system is integrated with NCI’s registry of eligible clinical investigators (RSS) to ensure that experimental agents are only sent to qualified clinicians. The GOG is using this process on two large-scale, Phase III protocols, with a combined accrual of 1,901 patients, totalling 3,419 drug orders/reorders from over 300 different GOG affiliated institutions and over 560 different GOG affiliated physicians.

RETENTION OF CLINICAL TRIAL PARTICIPANTS IN A STUDY OF NON-GONOCOCCAL URETHRITIS (NGU), A SEXUALLY TRANSMITTED INFECTION
Jeannette Lee, Shelly Lensing, Jane Schwebke
Little Rock, AR, USA; Birmingham, Alabama, USA

Retention rates of clinical trial participants are influenced by demographic characteristics, symptoms, and participant perceptions regarding the importance of treatment for their long-term health. NGU is the most common urethritis syndrome seen in men in the U.S. and up to 40% of cases have been attributed to Chlamydia trachomatis. Trichomonas vaginalis is a potential etiologic pathogen for NGU. Currently recommended treatments for NGU are azithromycin (A) and doxycycline (D). The NIH-sponsored Sexually Transmitted Infections Clinical Trial Group (STI CTG) conducted a clinical trial to determine if the addition of tinidazole (T), an agent with activity against T. vaginalis, would improve clinical cure rates. Study participants were randomized to receive A, A+T, D, or D+T. Follow-up visits occurred at days 15-19 and 35-45. Study participants were heterosexual men aged 16-45 attending sexually transmitted disease (STD) clinics. NGU was defined as new onset urethral discharge or dysuria and a urethral smear with > 5 polymorphonuclear leukocytes (PMNs) per 3-5 oil immersion fields without evidence of gonorrhea. The study recruited 305 participants with an average age of 27 years. Almost all were non-Hispanic African-Americans. Of the participants, 23% did not have a high school degree, 46% had a high school or GED degree, and 31% had attended or completed college. The overall retention rate through the 2nd follow-up visit was 68%. It did not vary with age or treatment, and was positively correlated with educational level. The effect of symptoms on retention was mixed. All participants with urethral discharge at first follow-up were retained in the study by second follow-up in comparison to 78% without discharge. Only 33% of those reporting recent skin rash at baseline completed the study; 71% of those without skin rash completed the study. Retention of clinical trial participants with STIs is a challenging issue.
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GYNECOLOGIC ONCOLOGY GROUP (GOG): REMOTE PAPERLESS STUDY CHAIR REVIEWS
Angela Kuras, Bette Stonebraker, William E. Elgie, Josh Killion, Kareem Kouis, John Blessing
Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, USA

The Gynecologic Oncology Group (GOG) is a multi-institution, multi-discipline Cooperative Group funded by the National Cancer Institute (NCI) to conduct clinical trials which investigate the treatment, prevention, control, quality of survivorship, and the biology of gynecologic malignancies. The GOG Statistical and Data Center (SDC) collects patient data electronically via the SDC Electronic Data Entry System (SEDES). This collection of electronic CRFs enables the SDC Clinical Data Coordinators and Study Chairs to review summaries of key data items. Paper based reports, such as operative reports and pathology reports, are scanned and stored electronically in SEDES. The Study Chair assigned to each GOG trial is responsible for conducting a review of patient charts to evaluate protocol compliance including: determination if the protocol treatment was administered on schedule; assessment of dose adequacy; the appropriateness of dose modifications; and review of adverse event and tumor response data. In the past, all Study Chair reviews were conducted in the GOG SDC office in Buffalo, NY using paper charts. The SDC recently developed an application that allows the Study Chair to conduct a remote paperless review of the electronic data. This application is a secure, password protected portal to the GOG patient charts. The application includes summaries of key data items, scanned reports, modality review sheets, query letters, and eligibility checklists. After the review has been conducted, the Study Chair enters the results of the review and notes directly into the application. The Study Chair can also generate query letters in the review application. The details of the remote paperless study chair reviews will be presented.

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POWER ANALYSIS OF NOMINAL AGREEMENT AMONG MULTIPLE RATERS
Zhibao Mi, Kousick Biswas, Joseph Collins
VA Cooperative Studies Program, Perry Point, MD, USA

It is common practice that certain information collected in clinical trials, such as data extracted from radiation imaging, histology sections, etc., needs to be validated by multiple raters, and this type of data can be analyzed using the generalized Fleiss kappa statistic. However, the powers of these analyses are often neglected and untested. We propose to estimate sample size and perform power analysis for the kappa statistic. A SAS program was written to perform power analysis for testing kappa, and sample size estimation based on either pilot study data or key information from an experimental design that includes number of raters (m), number of categories (c), estimated marginal proportions (p) of number of subjects (n) independently classified by m raters into one of c categories, and projected kappa statistic. Asymptotic variance was calculated according to Fleiss (1971), and the null hypothesis was defined as each data point of a subject being classified into each category by m raters with common marginal probabilities of 1/c. Several hypothetical scenarios were tested to validate the program using multinomial parameters of m and p = (p1,...,pc) for c categories as well as actual data that Fleiss used to illustrate the kappa statistic. The results showed that both sample size calculation and power analysis were stable. The method can be applied to one-sided and two-sided hypothesis tests for either one sample or two sample kappa statistic testing designs. However, the adequacy of the method depends on the use of a large sample of estimates of variance, the approximate normality of the distribution of kappa, and independence among the raters’ evaluations.

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SINGLE-VISIT SCALE AND POLISH FOR GINGIVAL HEALTH:
THE RESULTS OF A PRACTICE-BASED RCT
Presenting Author: Clare Jones¹
Co-authors: Keith Milsom¹, Philip Ratcliffe², Annette Wyllie², Tatiana V. MacFarlane³, Martin Tickle¹
The University of Manchester, Manchester, UK; ²NHS Wirral, UK; ³University of Aberdeen, UK

'Scale and polish' aka 'oral prophylaxis' is commonly prescribed by dental practitioners and has become inextricably linked with the routine dental check-up. Despite its popularity, there is no evidence to support the effectiveness of the intervention or frequency at which it should be provided. The vast majority of research into scale and polish effectiveness has been carried out in academic or specialist institutions, yet most dental treatment
is provided in primary care dental practices which have a different patient demographic.

A practice-based parallel randomized controlled trial with 24-month follow-up was conducted. Healthy adults (BPE codes <3) were randomly assigned to 3 groups (6-month, 12-month, or 24-month interval between scale and polish). The primary outcome was gingival bleeding with the hypothesis that 6-monthly scale and polish would result in lower prevalence than 12-month or 24-month frequency. Follow-up measurements were recorded by examiners blinded to the allocation. 125, 122 and 122 participants were randomized to the 6-month, 12-month and 24-month groups respectively. Complete data set and multiple imputation analyses were conducted.

Prevalence of gingival bleeding at follow-up was: 84% (6-month); 78% (12-month); and 82% (24-month). The differences between groups were not statistically significantly different (p=0.746). Statistically significant differences were not found between groups for follow-up prevalence of plaque and calculus. The statistically significant differences in the amount (mm) of calculus between groups at follow-up were not clinically significant. Patients who received treatment every 6 months were significantly more likely to report high levels of oral cleanliness than those in the 12-month or 24-month group.

This trial casts doubt on the health benefits provided by 6-monthly single-visit scale and polish over 12- or 24-month frequency, for patients with BPE <3, and informs future practice-based research on this subject.

**P67**

**CONDITIONAL POWER USING AN INFORMATION BASED APPROACH TO DETERMINE FUTILITY IN EQUIVALENCE TRIALS**

**Uma Kher, Aditi Sapre**

*Merck & Co., Rahway, NJ, USA*

The power of a study assesses whether a clinical trial is likely to yield useful, interpretable data given the targeted sample size. Very low power means that the trial may be futile, i.e., unlikely to reach statistical significance even if the alternative hypothesis is true. Although one never initiates a trial that is believed to be futile, futility can be assessed during the course of a trial. There are a number of metrics that can be used to assess futility with conditional power being one of them. Conditional power quantifies how unlikely it is to reach a statistically significant result at the end of the study given specific assumptions about the pattern of data to be observed for the remainder of the trial; it is the probability of observing a statistically significant benefit at the end of the trial conditional on the data observed at a pre-specified interim timepoint. The assessment of conditional power at an interim analysis can be used to not only terminate a potentially unsuccessful study but also to potentially suspend the initiation of resource intensive activities across the drug development program. Our research examined the conditional power framework for an equivalence trial with a pre-specified interim analysis for futility, under assumptions of unequal sample sizes in each group, using an information based approach. Simulations were run to assess the impact of various unknown parameters (e.g. ratio of sample sizes, variability, timing of the IA, distribution of the outstanding data) on the Cp.

**P68**

**CHALLENGES IN THE DESIGN AND CONDUCT OF CONTROLLED CLINICAL EFFECTIVENESS TRIALS IN SCHIZOPHRENIA**

**Robert Rosenheck, John Krystal, Robert Lew, Paul Barnett, Soe Soe Thwin, Louis Fiore, Danielle Valley, Grant Huang, Carla Neal, Julia Vertrees, Matthew Liang for the CSP 555 Research Group**

*Veterans Affairs (VA) Connecticut Healthcare System, West Haven, CT, USA; Yale School of Medicine, New Haven, CT, USA; Massachusetts Veterans Epidemiology and Research Information Center (MAVERIC) Cooperative Studies Program Coordinating Center (CSPCC), Boston, MA, USA; VA Health Economics Resource Center, Menlo Park, CA, USA; VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM, USA; Cooperative Studies Program Central Office, VA Office of Research & Development, Washington, DC, USA*

Background: The introduction of antipsychotic medication has been a major advance in the treatment of schizophrenia and allows millions of people to live outside of institutions. It is generally believed that long-acting intramuscular antipsychotic medication is the most effective approach to increasing medication adherence and thereby reduce relapse in high-risk schizophrenia patients but the data are scant. Purpose: To report a study
design to assess the effect of long-acting injectable risperidone in unstable patients and under more realistic conditions than previously studied and to evaluate the effect of this medication on hospitalization, schizophrenia symptoms, quality of life, medication adherence, side effects and costs. Methods: The trial was an open randomized clinical comparative effectiveness trial in patients with schizophrenia or schizo-affective disorders in which parenteral risperidone was compared to oral antipsychotic regimen selected by each control patient's psychiatrist. Participants had unstable psychiatric disease defined by recent hospitalization or need for psychiatric services. The primary endpoint was psychiatric hospitalization; the secondary endpoint was psychiatric symptoms. Results: 382 patients were randomized. Determination of competency to understand informed consent was addressed. Use of closed circuit TV interviews for psychosocial measures provided an economical, quality, reliable means of collecting data. A unique method for insuring that usual care was optimal was incorporated in subject follow-up. Limitations: VA patients with schizophrenia or schizo-affective disorders and with co-morbid illnesses are a challenging study group in long-term trials. Some techniques unique to VA and found useful may not be generalizable. Conclusions: The trial tested an antipsychotic medication early in its adoption in the Veterans Health Administration. The VA has a unique electronic medical record and database which can be used to identify the primary endpoint with complete ascertainment. Several methodologic solutions addressed competency to understand elements of consent, the costs/reliability of interview data gathering, and insuring usual care.

P69
STRATEGIES TO MAXIMIZE ENROLMENT FOR TRIALS REQUIRING IN-HOSPITAL POSTPARTUM/POSTNATAL RECRUITMENT
Katherine Trigiani, Johanna Sanchez, Elizabeth Asztalos
Centre for Mother, Infant, and Child Research (CMICR), Sunnybrook Research Institute, Toronto, Ontario, Canada

In-hospital recruitment is an economical and efficient way to enroll postnatal/postpartum patients in trials, and may be required by the study protocol. However, the brief hospital stay, particularly for uncomplicated pregnancies, presents a particular challenge to recruitment; among other issues, it can be difficult to harmonize recruitment quotas with ethical considerations in the vulnerable postpartum population.

The first step is to identify the ideal location for recruitment; for example, is the target population most likely to deliver in the LBRP (labour, birth, recovery, postpartum), the high-risk unit or the maternity ward? Second, identify the ideal time to recruit; being aware of activities such as breastfeeding classes and usual hospital discharge time will decrease missed opportunities. Third, schedule blocks each day to leave study information with all eligible mothers, drop by to answer questions, and collect all consent forms and other study materials. Fourth, make the charge nurse aware of the study and schedule time each morning with him/her to identify eligible participants, as well as to become aware of patients experiencing complications. Finally, the recruiter should obtain access to patient charts to identify mothers who have just delivered. Potential participants should be approached as soon as possible, as maximizing the time between approach and hospital discharge reduces pressure on the mother’s decision. Ideally, early contact will allow the recruitment materials to be left with the family overnight.

The result of these strategies is a higher rate of enrolment. Maximizing time for parents to become familiar with the material and prepare questions for the recruiter increases the likelihood of informed consent and decreases the probability of losing the patient during follow-up.

P70
EXPLORING THE POTENTIAL FOR INCONCLUSIVE RESULTS FROM A NON-INFERIORITY TRIAL
Allison R. Edwards for the Diabetic Retinopathy Clinical Research Network (DRCR.net)
Jaeb Center for Health Research, Tampa, FL, USA. Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EYO18817.

Purpose: For any non-inferiority trial, there is the possibility of finding (1) drug A is not non-inferior to drug B and (2) drug B is not superior to drug A, i.e., inconclusive results. We explored the potential range of observed values for which this might occur in a DRCR.net trial currently under development to test whether one drug is non-inferior to a second drug.

Methods: Using a fixed sample size (based on a clinically relevant non-inferiority margin) and an estimate of expected standard deviation that was also used for the sample size calculation, two one-sided 95% confidence
bounds were constructed around each of a range of possible observed mean differences. These bounds were then reviewed to determine for which observed differences the upper bound is greater than the chosen non-inferiority margin and the lower bound is less than zero.

Results: For the DRCR.net trial, which is evaluating visual acuity letter score as the primary outcome and for which the non-inferiority margin was chosen to be 3 letters, the exercise found an observed mean difference between 1.4 and 1.6 letters would result in an inconclusive study. Given the same standard deviation, if a non-inferiority margin of 4 letters was selected and sample size adjusted accordingly, an observed mean difference between 1.8 and 2.2 would result in an inconclusive study.

Conclusions: Inconclusive findings occur when the observed mean difference is close to the midpoint of the non-inferiority margin and zero. Considering the range of possible observed values under which inconclusive results from a non-inferiority trial could occur is a useful exercise which could influence choice of non-inferiority margin and sample size, and thus help avoid a wide inconclusive range that contains clinically important differences.

**P71**

**TRANSFERRING RANDOMIZED PARTICIPANTS - THE ACCORD MODEL**

Sharon K. Wilmoth, Jason Griffin

Wake Forest University Health Sciences

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to test three medical strategies for reducing cardiovascular events in 10,251 participants randomized through 77 clinics across the United States and Canada. The clinical sites were administratively located under 7 Clinical Center Network (CCN). With clinical sites being in various geographic locations across North America, an efficient process to deal with those participants who needed to move out of the area but wished to remain in the trial and attend another clinic for their clinic visit is essential.

There were several procedural steps that needed to occur that involved communication among the CCNs, the clinical sites and the Coordinating Center before the database could be changed to reflect the move. Once the transfer was established, a notice was emailed to all the study units involved, which included the CCN, the clinical site, the Drug Distribution Center, the ECG Reading Center, and the company that provided diabetic supplies. Ancillary Substudy personnel involved in the ACCORD MIND Substudy or the ACCORD Bone study were also notified if the participant was participating in one of these substudies.

Participant ID numbers reflect the CCN and clinical site (CS) number and take the form ABBC#####, where A is the number representing the CCN, BB is the number representing the clinical site (CS) number within the CCN. The 5 digit number preceded by an alphabetical character references the participant within the study. The participant ID stays with participant throughout the study. If a participant changes CCN or CS, then the first two prefixes (A and BB) will change to reflect the new status. The last 6 digits of an ID will not change. The poster presentation will outline and describe the steps involved in the transfer of ACCORD participants from one clinic to another.

**P72**

**DATA AND SAFETY MONITORING IN NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID) CLINICAL TRIALS**

Susanna Weiss, Dennis O. Dixon, Kelly Cahill, Lawrence Fox,

Joni Love, James McNamara, Lydia Soto-Torres

National Institute of Allergy and Infectious Diseases (NIAID);
National Institutes of Health (NIH); Bethesda, MD, USA

In July 2009, the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) adopted a revised *Policy on Data and Safety Monitoring Board (DSMB) Operations.* We describe the considerations and process that motivated this step, in the hope that other organizations may benefit from our experience. Within NIAID there are four divisions that manage clinical trials and oversee data and safety monitoring for those trials: the Division of Acquired Immunodeficiency Syndrome (DAIDS), the Division of Allergy, Immunology, and Transplantation (DAIT), the Division of Clinical Research (DCR), and the Division of Microbiology and Infectious Diseases (DMID). Historically, the four operated largely independently and autonomously with respect to their approaches to data and safety monitoring. However, while some program variances may be
appropriate and/or necessary, as occasions for direct collaboration have increased, NIAID has recognized the need for harmonization of policies and procedures among the divisions. From 2005–2009, a working group undertook a review across NIAID, covering DSMB responsibilities, structure and operation, and the regulations, policies, and guidance documents governing their use. We summarize the final policy document that the working group produced; provide tabular cross-sectional overviews of how the NIAID divisions are harmonizing their DSMB operations, and highlight some recommendations for successful use of DSMBs. At NIAID, the institute-level policy document provides a collective understanding of the important contribution that DSMBs make to the responsible conduct of clinical trials. Over time, thinking will continue to evolve, leading to further policy refinements and the continued assurance of patient safety in our clinical trials.

*Available at: http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Documents/dsmbpolicyv3.pdf

P73
A UNIQUE WEB-BASED TOOL FOR PERFORMING AND TRACKING DATA QUALITY ASSURANCE TASKS IN A MULTI-CENTER STUDY
Kathy Clingan, Brenda Brewer, Michael Florczyk, Merwyn Lasrado, Nancy Payte, Jennifer Rosenbaum
Westat, Rockville, MD, USA

The National Lung Screening Trial (NLST) is a randomized controlled trial designed to determine whether screening with low-dose helical computed tomography reduces lung cancer mortality relative to screening with conventional chest x-ray in persons at elevated risk of lung cancer. As the coordinating center (CC) for NLST's Lung Screening Study component (NLST/LSS), we are responsible for systems development and central database management for ten sites that enrolled 34,614 participants, with the goal of ensuring the production of quality data. The NLST/LSS utilizes the Integrated Data Entry and Administration System (IDEAS), a distributed study management system that supports remote data entry with nightly replication of data from site servers to the central database. IDEAS performs standard data quality assurance (QA) tasks including front-end logic checks and forms tracking but lacks a mechanism for performing edit check overrides and back-end logic checks. Initially, these data QA tasks were handled manually by distributing edit forms to sites using e-mail or regular mail. However, with time and an increase in data volume, the need arose for a more efficient and cost-effective approach.

In response, we designed a user-friendly Web-based data QA system that enables CC staff to generate and upload pre-programmed data cleaning tasks for immediate viewing, printing, and resolution by sites. In addition, nightly interaction with the IDEAS database facilitates swift task close-out, resulting in more timely availability of cleaned data. This presentation will highlight the unique features of this efficient tool, illustrate how its implementation has streamlined the data QA process for NLST/LSS, and explore the lessons learned along the way.

P74
CREATING A BETTER, SHORTER DMC REPORT: A STACK OF NEEDLES, NOT A NEEDLE IN A HAYSTACK
David Kerr
Axio Research, Seattle, WA, USA

Data Monitoring Committees (DMCs) are now standard for Phase 2 and Phase 3 clinical studies. A DMC is a group of 3-6 independent clinicians and statisticians who meet regularly during the course of the study to ensure the study is still ethical to continue by focusing on protecting the safety of trial participants, the credibility of the study, and the validity of study results.

Based on 15 years of experience with the production of DMC reports, we would like to share our insights into what distinguishes an effective DMC report from an ineffective one. Because DMC members have a limited time to review the report prior to the DMC meeting, exhibits should be designed to focus on safety signals or to establish the lack of safety signals as briefly as possible. The abridged report shows a signal or appendices can be provided in a searchable format along with the report.

Additionally, there are aspects of DMC monitoring that are intrinsically related to the real-time nature of reviewing a live database where data are still being actively entered and where the data have not been fully cleaned. For all trials, and especially for those with formal interim stopping bounds, metrics about the amount of information
that is in the field but not in the database is critical to sound decision making. These types of summaries might also be useful for sponsor teams to review in a blinded fashion during the course of the study.

We will present our suggested Table of Contents for a 100-page DMC Report with examples of the tables, listings, and figures (TLFs) that we think give the DMC the essential information for their review, without unnecessary reports that would distract from the DMC’s primary responsibilities.

P75
REGIONAL COLLABORATORS’ MEETINGS FOR AN INTERNATIONAL STUDY
Sonya Mergler, Dalah Mason, Johanna Sanchez, Jon F. R. Barrett, Elizabeth Asztalos
The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Toronto, Ontario, Canada

The Twin Birth Study (TBS) is a multicentre, international, randomised controlled trial (RCT) with 97 actively recruiting centres in 25 countries with a recruitment goal of 2800 patients. The study seeks to determine 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.

The trial initially planned to hold several large international collaborators’ meetings during the conduct of the study. The purpose of these meetings was to provide collaborators with a study overview and update, as well as to promote collegiality. However, these meetings were costly and the large number of participants involved limited collaborators opportunity to engage in discussion. As a result, a decision was made to hold smaller regional meetings instead.

Smaller geographically focused meetings were held in the respective regions which included sites in Australia, Europe and the Middle East, North America, and South America. In addition to presenting the study overview and update, recruitment challenges experienced by the sites were shared, and approaches to gaining additional study sites were discussed. A major component of these meetings was the discussion of strategies for stimulating recruitment as well as methods of disseminating these ideas to all TBS sites.

These smaller regional meetings were more cost-effective due to reduced travel and accommodation expenses. In addition, the meetings were more personal and therefore more effective in: motivating centres to recruit trial participants, find new centres, and raise enthusiasm. Collaborators were also able to engage in open discussion about common regional challenges and solutions.

P76
DESIGN AND IMPLEMENTATION OF A NEW QUERY MANAGEMENT SYSTEM
Cathy Yang, Michael Shi, Elizabeth Asztalos
The Centre for Mother, Infant, and Child Research Sunnybrook Research Institute Toronto, Ontario, Canada

The Centre for Mother, Infant, and Child Research (CMICR) is the data and clinical coordinating centre for multi-centre randomised controlled trials (RCTs). In order to validate and clean data, discrepancies are identified and queries are sent to the recruiting sites. Generating, tracking, and managing those discrepancies can be challenging without the right software tools.

Previously at CMICR, there were several programs assisting in the query process. However, due to communication barrier between systems, paper based query reports had to be manually created for each site to collate the discrepancies from all resources. In order to prepare those reports, the research coordinator and assistant often spent hours photocopying the patient’s forms and writing out notes each month.

A new query management system was designed and developed to efficiently identify and manage all discrepancies and automatically generate the query reports. In this system, a Microsoft® Access database stores and manages all the edit checks and the identified discrepancies; a SAS® program merges patient data of the trial and generates all the discrepancies into the Microsoft® Access database; Visual Basic Applications (VBA) procedures in Microsoft® Access and Excel automatically create and export the query report into an Excel workbook for each site.

This new system allows for the effective and detailed management of the discrepancies and automation of the query reports, thus, greatly reducing the query process time. It also leads to electronic delivery of the query reports and query solutions and improves overall data quality.
P77
DOUBLE DATA ENTRY QUALITY CONTROL IN URECA (URBAN ENVIRONMENT AND CHILDHOOD ASTHMA), A MULTISITE LONGITUDINAL STUDY
Stephanie Hicks, Pat Zook, Rich Budrevich, Ryan Bailey, Cynthia Visness, William Taylor, Michelle H. Walter for the Inner City Asthma Consortium
Rho, Chapel Hill, NC, USA

INTRODUCTION: Accuracy of data entry is essential for obtaining valid results in a research study. Double data entry (DDE) is a tool to assess data entry error rates and ultimately improve data quality. The Urban Environment and Childhood Asthma (URECA) is a multi-center, prospective birth cohort study in which data entry occurs at the research sites using a web-based data management system (DMS).

METHODS: The URECA DMS randomly selects 5% of specified data forms. Copies are sent to the Statistical and Clinical Coordinating Center (SACCC) for repeat data entry. Standardized reports show overall error rates and rates by site, by form, and by staff person.

RESULTS: Five rounds of double data entry have been performed in the URECA study. The overall error rate has decreased over time from 0.95 percent in the first round of DDE (9,705 fields sampled) to 0.19 percent in the fifth round (11,649 fields sampled). DDE has also helped to identify difficult forms and staff members who may have trouble with data entry. The site-specific error rates have decreased, as have error rates for complicated forms.

CONCLUSION: The DDE quality control measures of the URECA study show that data entry has improved as the study has progressed. This is likely due to staff stability and revisions to forms with high error rates, as well as ongoing electronic data checks and SACCC feedback. The utilization of DDE, along with electronic data checks, site visit spot checks, conference call discussions, and data entry certifications are all worthwhile mechanisms to ensure quality study data.

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P78
THE PROCESS OF DEVELOPING AN ONLINE RANDOMIZATION SYSTEM
David Lau, Michael Shi, Johanna Sanchez, Elizabeth Asztalos
The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Toronto, Ontario, Canada

The Centre for Mother, Infant, and Child Research is the coordinating centre for several international randomised controlled trials (RCTs). The randomisation of patients for these RCTs is done with an automated phone system. As more trial related activities move from paper-based to electronic data capture (EDC), the demand for an online randomisation system increases due to its accessibility and convenience.

We will discuss the decision to move towards an online system and our exploration with various technologies to host or build the system. Specifically, we will discuss our experiences with third party vendors and in-house possibilities with Microsoft Infopath, Sharepoint Webparts and ASP.NET.

Based on the low cost, familiarity with the programming language, and resources available online, it was determined that building an in-house system using the ASP.NET technology was the best option. The third party trial management solutions we considered were found to be costly or did not offer a randomisation component. Infopath had the ability to setup user interfaces quickly, but was difficult to code and customize. Sharepoint Webparts was more customizable, but since we did not administer the environment we would lose control of the solution after deploying, therefore making it difficult to modify.

Based on our experience, ASP.NET was the best option to build the online randomisation system. This was only after experimenting with several different technologies and weighting important factors such as cost, functionality, familiarity, resources, and support.
Longitudinal studies normally identify and adjudicate incident events detected during follow-up by retrieving medical records. There are several reasons that the adjudication process may not be successfully completed for a suspected event including inability to retrieve medical records from hospitals and an insufficient time between the suspected event and data analysis. These incomplete adjudications are normally assumed not to be events, an approach which may be associated with loss of precision and introduction of bias. In this manuscript we evaluate the use of multiple imputation methods designed to include incomplete adjudications in the analysis. We demonstrate that this approach may increase precision and reduces bias in estimates of relationships between risk factors and incident events.

A CASE FOR USING ABSOLUTE TREATMENT DIFFERENCES WHEN DESIGNING A CLINICAL TRIAL WITH A DICHOTOMOUS OUTCOME

Tony Panzarella
Princess Margaret Hospital, Toronto, Canada

An important consideration when designing a randomized clinical trial (RCT) is the calculation of the sample size required to demonstrate a difference of interest, often between two groups, a control group C, and an experimental group T. Group differences involving proportions pC and pT, are usually conveyed in either absolute terms (pC - pT) or as a relative difference (pC - pT) / pC. For example, if pC = 0.80 and pT = 0.60 the absolute difference would be 0.20 while the relative difference is 0.25. If we assumed a control proportion in the sample size calculation that turned out to be inaccurate we wanted to understand which approach was less sensitive to such an error.

To this end we considered several hypothetical 2-armed RCTs, and using a standard sample size formula for a dichotomous outcome, determined the sample size to detect a relative difference between the groups C and T and the corresponding absolute difference. Tables of the number of patients required as a function of the control group event rate, pC were generated. We found that the effect of inaccuracies in the control group event rate were more sensitive if we sought to maintain a constant relative improvement compared to a constant absolute improvement. The results also indicated that the level of inaccuracy was a function of the control group event rate.

We discuss the ramifications of this finding, and conclude that mitigating the effect of an inaccurate control group event rate is better achieved by using absolute treatment differences when designing an RCT.

THEORETICAL ERROR RATES OF QUALITATIVE UDS TESTS FOR STIMULANTS

Neal Oden, Paul VanVeldhuisen
Rockville, MD, USA

Clinical trials in stimulant abuse and addiction often use a urine drug screen (UDS) to help measure abstinence, often part of the primary outcome. A qualitative UDS is usually considered positive if benzoylecgonine (BE) concentration in the urine exceeds 300 ng/mL. In a clinical trial setting, a positive qualitative UDS (on day 0) is typically interpreted as a study participant having used stimulants at least once during days -1 to -3, while a negative qualitative UDS is interpreted as no stimulant use on those days.

There are at least two potential sources of error in this approach. The first, which involves the laboratory analysis, concerns the accuracy with which the UDS test detects BE. The second, which is more concerned with human behavior, hinges on whether a high BE concentration on day 0 is reliably associated with drug-taking behavior on days -3 to -1. We ignore the first source, and attempt to determine theoretical error rates associated with the second source.
Li et al. express BE concentration in urine as a function of drug use and time since use. An implication is that, because BE clears so quickly, UDS results depend mostly on time since most recent dose. We used the relationship between BE concentration in urine and time since drug use in conjunction with assumptions about typical behavior of study participants in addiction trials to derive theoretical curves for the sensitivity, specificity, positive predictive value, and negative predictive value of assigning a study participant as having used stimulants over days -3 to -1, as a function of probability of daily drug use. Under these assumptions, the probabilities of false negative and false positive, when averaged over time or participants, are not likely to be more than 0.10.

**P82**

**EFFECTIVE GRAPHICAL DATA DISPLAYS TO FACILITATE EXPEDITED DSMB REVIEW OF CLINICAL TRIAL DATA**

Karen Boyle, Katharine Poole

*Rho, Inc. Chapel Hill, NC, USA*

The Statistical and Data Coordinating Center (SDCC) at Rho is responsible for creating materials for Data and Safety Monitoring Board (DSMB) review for many studies for the Immune Tolerance Network (ITN) project. Fifteen studies in this network are reviewed by four different DSMBs based on therapeutic category: autoimmunity, type 1 diabetes, asthma/allergy, and solid organ transplant.

Since the primary purpose of the DSMB is to ensure the safety of the subjects in the trial, it is important to create materials containing a large amount of information in a way that facilitates expedited review. In order to gain a clear understanding of the study data and have minimal displays, Rho creates graphical displays whenever possible. Supporting tables and listings are included with the DSMB materials to provide additional details; however, we have found that these tables and listings are seldom utilized when informative graphical displays are provided.

Several graphical displays have been developed to illustrate subject visit status, to show the timing of important clinical events in relation to study intervention, to allow for comparison of clinical data from various data streams, and to summarize trends while showing troublesome outlying data. Examples of graphical displays will be shown and described on the poster. These figures were created using the SAS® system software version 9.1 (or higher). Many of these figures could be utilized for clinical trials across therapeutic areas to facilitate DSMB review.

This project is funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under contract HHSN272200800029C.

**P83**

**CLUSTERING IN SURGICAL TRIALS: DATABASE OF INTRA-CLUSTER CORRELATIONS**

Jonathan Cook1, Thomas Bruckner2, Graeme MacLennan1, Christoph Seiler3

1Health Services Research Unit, University of Aberdeen, UK; 2Institute of Medical Biometry and Informatics, Heidelberg, Germany; 3Study Center of the German Surgical Society, Heidelberg, Germany.

Background: Patients under the care of the same surgeon will be influenced in a similar manner due to the surgeon's practice, skill and experience. Outcomes for those treated by the same surgeon tend to be similar. This phenomenon is referred to as the clustering effect and is quantified by the intra-cluster correlation (ICC). It impacts upon both the sample size requirement and statistical analyses of RCTs. Whilst these consequences are widely accepted for cluster trials, it is only recently that the potential implications for surgical trials have become acknowledged. However, trialists have little data upon which to assess the impact and base trial design.

Aim: To quantify the clustering effect in a database of surgical trials and demonstrate approaches to adjusting the sample size and statistical analysis.

Methods: ICCs were calculated for outcomes from a set of 10 surgical trials using an ANOVA approach with bootstrapped confidence intervals. Clustering was assessed at both centre and surgeon levels. Trials covered general, ophthalmic and orthopaedic surgical specialties. Outcomes evaluated included surgical, clinical and patient reported (including quality of life) measures.

Results: Outcome type and follow-up period appeared to influence the ICC value though uncertainty around individual estimates was substantial. Plausible impact of empirical ICCs on sample size varies from no to small
increase for patient reported outcomes (e.g. 0-5% for EQ-5D) to a substantial increase for short-term clinical outcomes (e.g. 8-14% for operation time).

Conclusions: This set of empirical surgical ICCs provides trialists with valuable information on the magnitude of clustering effect enabling incorporation into trial design. Trialists should included ICCs in surgical trial reports and consider contributing trial datasets to a database.

**P84**

**ADJUDICATION OF VISUAL FIELD ENDPOINTS IN THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS)**

Mae Gordon, Dale Heuer, Eve Higginbotham, Richard Parrish, Patricia Morris, Bradley Wilson, Julie Beiser, Michael Kass for The Ocular Hypertension Treatment Study

Washington University School of Medicine, St. Louis, MO, USA

Visual field loss is a primary outcome measure accepted by the FDA for the success of preventing or treating glaucoma. In the Framingham Eye Study (mean age of 65 years), the prevalence of other ocular conditions capable of causing visual field loss (cataract 12.3%, age-related macular degeneration 5.7% and diabetic retinopathy 1.8%) collectively far exceed the 1.9% prevalence of open angle glaucoma. The Ocular Hypertension Treatment Trial (OHTS) is a randomized clinical trial of the safety and efficacy of topical ocular hypotensive medication in the prevention of primary open angle glaucoma (POAG). OHTS is the only National Eye Institute trial of glaucoma treatment to use an endpoint adjudication committee. We report the impact of endpoint adjudication on estimates of POAG incidence, treatment efficacy and statistical power. Of the 1,636 participants randomized, 132 developed a visual field endpoint. Of the 132 visual field endpoints, the endpoint adjudication committee attributed 49% (65 of 132) to POAG and 51% (67 of 132) to other causes. The incidence of POAG was 4.0% (65 of 1,636) with adjudication and would have been 8.1% (132 of 1,636) without adjudication. The relative risk for treatment benefit was 0.44 (95% CI of 0.26 to 0.74) with adjudication and would have been .76 (95% CI of 0.55 to 1.06) without adjudication. Post-hoc statistical power estimated by a proportions test for independent samples was 0.88 with adjudication and would have been 0.37 without adjudication. Endpoint adjudication reduced bias in estimates of POAG incidence and treatment benefit and increased statistical power.

**P85**

**CONTROL GROUPS IN CAREGIVER INTERVENTION RESEARCH: ISSUES AND DILEMMAS**

Sara J. Czaja, Richard Schulz, Steven H. Belle

Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida, USA; Department of Psychiatry/University Center for Social and Urban Research, University of Pittsburgh, Pittsburgh, PA, USA; Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA

The documented personal, social, and health impacts of family caregiving have resulted in a large number of intervention programs designed to alleviate caregiver burden and distress. Despite the proliferation of these interventions they have only met with limited success for a variety of reasons. In this regard there has been an increased quest for evidenced-based treatments to improve caregiver outcomes which has increased the rigor of psycho-social intervention trials. Researchers are adopting clinical trial methodologies for intervention trials and incorporating a variety of control group conditions to provide a stronger evidence base for efficacious treatments. This enhanced rigor in research design has elevated the bar for intervention studies but at the same time increased the complexities of research designs and raised a number of methodological issues. This paper will discuss prevailing issues regarding the use of control groups in psycho-social caregiver intervention trials including: the need for control groups, types of control group designs, the challenges associated with control group design, ethical issues, economic considerations, and the potential impact of control groups on participant recruitment and retention and study outcomes. The focus will be on intervention trials for family caregivers of dementia patients. Examples are provided from a variety of caregiver intervention trials such as the Resources for Enhancing Alzheimers Caregiver Health (REACH) program. Specifically, we will characterize types of control groups that are being employed, how they vary with respect to intensity and the extent to which they represent actual treatments. We will also present data from a range of studies regarding the impact of varying control group designs on caregiver outcomes. Overall, these data suggest that control groups do have an influence study outcomes and that there is a need to identify the active ingredients in control conditions. Alternative designs for intervention trials will also be discussed.
CENTRAL STATISTICAL MONITORING IN CLINICAL TRIALS
Allan Hackshaw
University College London Cancer Research UK and UCL Cancer Trials Centre, UK

Background On-site monitoring is a common but time-consuming and expensive activity, with little evidence that it is worthwhile. Centralised statistical monitoring (CSM) is a much cheaper alternative, where data checks are performed by the co-ordinating centre, reducing the need to visit every site. Few publications have described the use of CSM in real clinical trials.

Methods R-programs were developed to check data at either the patient or site level, eg fraud. These included finding anomalous data patterns, digit preference, incorrect dates (eg weekends/holidays), values of variables too close or too far from the means, odd correlation structures and extreme variances. We applied these to 3 trials: (i) where data had already been checked, (ii) an ongoing trial where our findings could be checked in real-time, and (iii) where data errors and fake patients were created.

Findings The programs produced simple tables or figures. Few errors were detected in the trial where data had already been checked (as expected). Most data errors were found in the two other trials. The programs detected errors we created (eg fake patients with values too close to the multivariate mean; Figure 1a). They can also detect centres that have too few or too many serious adverse events (Figure 1b). However, there were difficulties in identifying outlying sites when a site had few patients (<5). Several examples of the different output produced, and how they are interpreted, could be shown and discussed, along with their strengths and limitations.

Conclusions CSM appears to be a cost-effective and worthwhile alternative to on-site monitoring. It could identify incorrect patient data, or sites where the data considered together is too different to all other sites and therefore should be reviewed. However, more research is needed to identify which situations CSM does not work well in.

SOME STRATEGIES FOR REPORT GENERATION BY BIOSTATISTICIANS IN CLINICAL TRIALS
Jon Yankey, Christopher Coffey, Bill Clarke
Iowa City, IA, USA

Reports are used to regularly monitor clinical trials (e.g., internal weekly reports to more formal reports for regulatory agencies). Simple reports are often generated directly through the distributed data entry system. However, more complex reports generally require the input of a biostatistician. There are several overriding thoughts when developing reports at the University of Iowa’s Clinical Trials Statistical and Data Management Center: A user friendly end-product is generally required, report generation needs to be automated as much as possible, and the software used to generate reports needs to be easily maintained and intuitive for other biostatisticians.

With these in mind, the following general strategies have been helpful:

* Develop a SAS program to be used up-front that places all relevant subject information in a single data set to be used by subsequent programs. This is advantageous because it ensures that the same set of subjects will be considered across tables.

* Develop one program per table/figure to be included in the report. PROC REPORT or a user-written macro is used to create tables in .rtf files. It is useful to use macro variables to assign the file paths for the .rtf files.

* Create a ‘master’ program that calls the individual SAS programs used to create the tables using %include statements (one statement for each program). This is advantageous because it is easier to open and run several separate programs. Here it is also useful to use macro variables to assign file paths for the individual SAS programs.

* Create a macro in MS-word that combines all the tables/figures into a single document.

This presentation will provide a more in-depth look at these strategies implemented using SAS and Microsoft office suite applications. As an example a weekly study report will be considered.
Multi-centered clinical trials can be extremely complex, with many components requiring a structured implementation to produce quality outcomes. The discipline of modern project management developed in the 1950s to meet competitive demands in the defense, engineering, and construction fields. Project management focuses on the use of multi-talented teams to solve problems and meet the complex expectations for a project a unique endeavor in a timely manner, fulfilling the desired scope within budget. The pharmaceutical industry has incorporated project management extensively in its administration of clinical trials; however, it has not been generally adopted in academic circles, where there is an equal need for the efficiency and structure this discipline offers. This presentation will discuss the implementation of beneficial project management tools and skills, particularly the project charter; communication plan; and deliverable work breakdown structure. Development of a project charter makes official the expectations of stakeholders, delineates roles and responsibilities of team members, and authorizes them to create a viable foundation for the study. The project charter, along with a clear understanding of the greater team concept (the internal and external people affected by the project), is an essential first step to establishing open, frequent, and concise communication. Communication, the essence of project management, is key in collaborative discussions addressing the development and planning of the project, including establishing a work breakdown structure and identifying the deliverables. If this planning is done well, the earned value, value of work performed in relation to the planned budget, can be explored. These are a few of the tools and skills that can be used by institutions involved in multi-center clinical trials. This project management approach, however, cannot just be implemented into isolated projects, but will need to be translated and integrated into this distinctive and demanding field of research.

HOW DO WE “ADAPT” THE ANALYSIS PLAN WHEN THE PROTOCOL IS MODIFIED?

Yuko Palesch¹, Myron Ginsberg², Michael Hill³, Claudia S. Moy⁴, Renee Martin¹, Sharon Yeatts¹

¹Medical University of South Carolina, Charleston, SC, USA; ²University of Miami, Miami, FL, USA; ³University of Calgary, Calgary, Canada; ⁴NINDS, Rockville, MD, USA

Most, if not all, clinical trials have protocol modifications sometime during the trial period. Many are for changing the eligibility criteria when subject recruitment is lagging or when unexpected safety issues arise. Some are for changing the clinical management to address compliance, safety, logistics, etc. When these changes are non-trivial (e.g., substantially changing the target sample profile, or changing the dose of the treatment), can and how do we adapt the statistical analysis plan (SAP) to reflect these changes, or do we start a new trial? We present one currently ongoing trial “Albumin in Acute Stroke (ALIAS)” to illustrate how such protocol changes were handled. The ALIAS Trial is an NIH-funded, multicenter, double-blinded, placebo-controlled Phase III trial to ascertain whether albumin confers neuroprotection in subjects with acute ischemic stroke. 434 subjects (of 1,800 required) had been randomized when the Data and Safety Monitoring Board (DSMB) recommended suspension of subject recruitment due to excess mortality in one group. At that time, the ALIAS Executive Committee was unblinded to the safety data in order to make changes to the eligibility criteria and clinical management. Ultimately, the Executive Committee, in consultation with the DSMB and the sponsor, deemed that the changes were substantial enough that the Trial could not continue as the same study, and a new ALIAS Trial began as Part 2 with the same primary hypothesis and primary outcome analysis based on Part 2 data only. The SAP has been modified to accommodate the changes, including the addition of meta analysis of the two trials. The process by which the decision was reached to start a new trial (rather than consider some adaptation to the analysis) will be presented.
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OPTIMIZING TRIAL MONITORING ON THE AZURE TRIAL

Geraldine Matthews¹, Roger Burkinshaw², Claire Davies¹,
Vicky Hiley¹, Helen Marshall¹, Rob Coleman²

¹Clinical Trials Research Unit, University of Leeds, Leeds, UK; ²Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

Determining how academic clinical trials units can optimise data quality via central monitoring methods is an important factor in trial management. In the AZURE trial, it became apparent from site monitoring that the end-point dates as defined in EORTC literature [1] were misinterpreted at site. Although a training programme was initiated, some sites were seen to report date of confirmation rather than date of onset/suspicion as required. Therefore the focus of site monitoring was changed to review this critical endpoint data. Due to limited trial monitoring resources, a pilot review of telephone monitoring was suggested. This pilot work reviewed 17 trial endpoints which had been verified by site and telephone monitoring. Agreement between site and telephone monitoring was achieved on 12/17 events. The success of telephone monitoring was strongly related to the experience of the person at site involved with the review. When talking to less experienced staff, it was difficult to remotely navigate through the notes and pick up earlier scans/ recurrences. Also, if a participant had more than one recurrence it was found to be difficult to piece together all the available information over the phone.

Telephone monitoring was implemented and a total of 105 events were reviewed, some cases with multiple queries. Agreement between telephone monitoring and the Case Report Forms was found on 81/105 events. In addition, 23 priority data queries were also identified for telephone monitoring which required clarification of diagnoses and addition of missing dates of suspicion with censoring of patients data if unresolved.

Our findings indicate that although site monitoring remained the gold standard method of source data verification, telephone monitoring is a useful method for validating endpoint data when site monitoring resources are not available.

References

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APPLYING FUTILITY ANALYSIS TO SEVERAL REAL CLINICAL TRIALS

Mark Jitlal, Iftekhar Khan, Allan Hackshaw

University College London Cancer Research UK and UCL Cancer Trials Centre, UK

Introduction: Phase III clinical trials are generally large and expensive, so stopping early for futility is a potentially attractive approach. It could avoid using further patients and funds on an ineffective intervention. We aimed to see how well futility methods perform for real clinical trials.

Methods: We retrospectively applied futility methods to 10 cancer trials that showed a large, only a moderate, or no effect (the target sample size was reached in all). The probability of finding a hazard ratio of the magnitude pre-specified at the start of the trial was calculated at specific time points (conditional power, CP), based on either number of patients or events, and allowing time for follow-up and analysis. CP <=15% could warrant early termination.

Results: Table 1 shows results from five of the trials. Futility analyses would, reassuringly, not have stopped either ABC02 (large effect) or even ZIPP (moderate effect). However, Study 12 only had low CP after 75% of patients had been recruited, but only a further 9% of patients (n=66) were left to be accrued. For Study 14, the CP was not low enough to stop early even after recruiting 75% of patients (CP=21%). If the analyses were performed after observing a certain percentage of target events, low CP was achieved in Study 12 and 14 after 50% deaths were seen, but only a further 12% or 0% of patients respectively would complete recruitment. TOPICAL might have terminated early, but a significant pre-specified subgroup effect could be missed (HR=0.74 females).

Discussion: Although futility might save resources, we show examples where the decision to stop early is so far into recruitment that it is not worth stopping (particularly with fast accrual rates). We provide more findings on all trials, including financial costs. The application of futility needs to be done with care.
RESOLVING DISCREPANT SLOPE ESTIMATES FROM SIMPLE LEAST SQUARES VERSUS REPEATED MEASURES REGRESSION

Brett Kaminski, Dongyuan Xing, Craig Kollman
Jaeb Center for Health Research Tampa, FL, USA

Background: Clinical trials often provide valuable data for secondary analyses to characterize the relationship between clinical measures. Repeated measurements from the same subject are often incorporated into these analyses to improve the precision of the estimated slope. However, slopes estimated from repeated measures (RM) models can be discrepant from those obtained by simple least squares regression (SLS).

Methods: We present data from two clinical trials demonstrating this phenomenon. In study A, the mean glucose (response) and the hemoglobin A1c (covariate) were measured at 3, 6, 9 and 12 months for each subject. In study B, central corneal thickness (response) and refractive error (covariate) were measured on both eyes of each subject. Separate between-subject and within-subject slopes were estimated by adding the subject covariate mean to the RM model.

Results: In study A, the estimated slope from SLS was 23.7 (95% CI= 21.2, 26.2) at 3 months and similar at other time points compared with 19.7 (18.4, 20.9) from RM. The estimated between-subject slope was 24.5 (22.6, 26.3) and the within-subject slope was 15.7 (14.0, 17.4).

In study B, the estimated slope from SLS was 0.99 (0.37, 1.61) using left eye data (similar for the right eye). The RM slope was 0.18 (0.24, 0.61). The estimated between-subject slope was 0.96 (0.31, 1.60) and the within-subject slope was 0.19 (0.73, 0.34).

Conclusions: Many RM analyses erroneously assume that the within- and between-subject slopes are identical. One symptom that this assumption may be violated is discrepant slopes from SLR and RM models. Including the subject covariate mean in the RM model is a useful technique to explore between-subject and within-subject effects.

SIMULATION STUDY OF AN INDICATION-FINDING TRIAL APPROACH TO PHASE II DEVELOPMENT

Heemun Kwok1,2, Roger J. Lewis1,3
1Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA; 2Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA, USA; 3Berry Consultants, LLC, College Station, TX, USA

BACKGROUND: After preclinical and phase I studies, a therapy may have potential benefit in multiple disease states. In this situation, a primary objective of phase II development may be to efficiently identify the disease(s) in which the therapy has a promising efficacy profile. An indication finding trial (IFT) is an approach in which a therapy is evaluated in multiple diseases simultaneously. A hierarchical model is used to borrow strength across the different diseases’ treatment effects. The objective was to compare the performance of an IFT approach with that of a conventional approach involving independent trials. METHODS: Our motivating example was infliximab, which is an anti-inflammatory agent with potential benefit in a variety of diseases. A hypothetical IFT of infliximab in nine diseases with group sequential monitoring was designed. Simulation was used to achieve desired operating characteristics in hypothetical scenarios with various assumed treatment response patterns. We then evaluated the design’s performance by simulating IFT’s of infliximab using historical data from published trials. For comparison, multiple, independent trials with conventional designs were also simulated. RESULTS: In the historical trials, the observed odds ratios comparing infliximab to standard therapy ranged from 0.32 to 24, with seven of the nine greater than one. The observed values were considered to be the true values for the simulation study. Based on 10,000 simulations, in the diseases with true positive effects, the IFT design demonstrated greater power than the conventional trials. In the two diseases with true negative effects, the IFT design had a higher type I error rate. The IFT design had smaller mean sample sizes in all diseases. CONCLUSIONS: In this simulation study, IFT’s had smaller mean sample sizes than conventional, independent trials, and their type I and II error rates were dependent upon the underlying heterogeneity of effect across diseases.
A Data and Safety Monitoring Board (DSMB) is responsible for ensuring the safety of subjects in clinical trials. There are five DSMBs that review studies for the National Institute of Allergy and Infectious Diseases (NIH/NIAID). These DSMBs meet several times a year and have many studies under their purview. DSMB attendees typically receive a hardcopy binder and CD-ROM for each study or for a group of studies under a single coordinating center. The number of binders and documents can be overwhelming considering the number of studies that may be reviewed during a meeting.

In collaboration with NIH/NIAID, Rho has created a website for the DSMB attendees to facilitate the distribution and review of materials. DSMB members are able to review documents for a specific meeting, view upcoming meeting agendas, and see a calendar of upcoming meetings. Administrators have the ability to create new DSMBs, assign protocols to a board, assign permissions for each user, create new meeting agendas, and upload documents for each meeting. To ease the transition to the web-based system, the layout of the agenda is designed to look like the hardcopy agendas with which they are familiar. Study information is linked to each of the agenda items.

The goals of this project are to save time and money by eliminating the need for hardcopy binders and CD-ROMs and to improve efficiency by having all meeting materials organized in one central, easily-accessible location.

This project is funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under contract HHSN272200800029C.

Background: Statistical procedures developed by Bland and Altman (1999) have become the standard for analysis of method comparison data. These methods rely on certain assumptions (normal distribution with no relationship between mean and variance) or transformation to meet assumptions. In practice, this is not always possible. The purpose of this presentation is to explore nonparametric methods that can be used in place of standard parametric procedures and illustrate them using visual acuity (VA) measurements obtained with manual refraction versus automated refraction. Substitution of automated refraction for manual refraction could result in substantial cost and time savings in ophthalmic clinical trials.

Methods: Electronic Early Treatment Diabetic Retinopathy Study Visual Acuity Test© letter score (EVA) was measured after automated refraction (AR-EVA) and after manual refraction (MR-EVA) in a multicenter study. As differences between AR-EVA and MR-EVA were not normally distributed, there was an apparent relationship between the VA level and the variance, and transformation was not successful, a nonparametric approach was applied to compare the 2 methods. These included using percentiles to describe the difference distribution, and use of rank transformation in regression analyses evaluating whether trends in method differences and variance were related to VA, and whether patient and disease factors affected agreement.

Results: Nonparametric analysis demonstrated that EVA obtained with automated refraction was worse than that obtained with manual refraction, with larger differences and greater variability found in participants with worse VA. It confirmed that these findings were not simply due to outliers present in the data that were more common with poor VA. Variability of differences also depended on autorefractor model, with Topcon 8000 series autorefractors resulting in AR-EVAs most similar to MR-EVAs.

Conclusion: Automated refraction obtained with Topcon 8000 machines can be used to substitute manual refraction in individuals with good visual acuity.
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USING OPEN SOURCE ELECTRONIC DATA CAPTURE FOR LARGE RANDOMIZED CONTROLLED TRIALS

Michael Shi, Johanna Sanchez, Elizabeth Asztalos

The Center for Mother, Infant, and Child Research, Sunnybrook Research Institute, Toronto, Ontario, Canada

The Centre for Mother, Infant, and Child Research (CMICR) is the coordinating centre for several large, international randomised controlled trials (RCTs). At CMICR, the data capture has traditionally involved distributing and collecting paper-based case report forms internationally. This paper-based process is time consuming and labour intensive, which prompted a search for a web-based system to minimize distribution and printing costs, and expedite the availability of accurate data for new research trials.

Taking into account personnel and financial resources, internal knowledge and expertise, and specific system requirements, a few approaches were considered: a) developing an in-house system, b) purchasing a commercial Electronic Data Capture (EDC) package, or c) pursuing an open source solution. For each approach, the following factors were evaluated: level of involvement/effort on system development, study start-up time, Infrastructure and administrative overheads, and the total cost of ownership (TCO).

After careful review of several EDC systems and consideration of developing an in-house solution, a decision for an open source EDC solution was made as it met the tight timelines, requirements and budget limitations, while also providing room and flexibility to accommodate various research trials in the future.

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DEVELOPING A FINAL ANALYSIS TIMELINE FOR A LARGE MULTICENTRE RANDOMIZED CONTROLLED TRIAL

Johanna Sanchez, Sonya Mergler, Dalah Mason, Kellie Murphy, Elizabeth Asztalos

The Centre for Mother, Infant, and Child Research (CMICR), Sunnybrook Research Institute, Toronto, Ontario, Canada

The Multiple courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) is a multicentre, international, randomised controlled trial for women who are at increased risk of preterm birth, designed to determine if multiple courses of antenatal corticosteroids decrease the risk of neonatal mortality or significant neonatal morbidity. Recruitment was completed in August 31, 2006 with 1858 women enrolled from 80 sites in 20 countries. At 18-24 months of age, follow-up data was collected on MACS children to assess for neurologic impairment. As we began to collect the final follow-up data for the last patients due in January 2009, it was planned that the results would be presented towards the end of the year, thus it was important to develop a final analysis timeline.

The database closure date was set for April 30, 2009 and the presentation of the results was scheduled for September 2009. This allowed for a four-month data campaign before database closure, and 10 months total to prepare the results.

A 10-month timeline was created, outlining key tasks broken down into months and weeks. From January to April, a data campaign was implemented to encourage sites to submit their data and resolve any outstanding data queries. As part of the campaign, data frequency analyses were scheduled to identify outliers. The frequency analyses were planned every six weeks to allow enough time to review and clarify outliers. Upon database closure and completion of the frequency analyses, a full data analysis was undertaken. Four full data analyses were scheduled to ensure the quality of the data. The data analysis was based on analysis tables created at the beginning of the trial.

This timeline was successful in ensuring data quality, and allowed us to meet our deadline. This presentation will share the approaches used in developing this MACS final analysis timeline.
CHALLENGE: The protocol for the FONT II Phase II clinical trial has required significant staged alterations to respond to newly emerging medication safety issues and recruitment concerns. Each revision required careful consideration in order to achieve a study design that is feasible and ethically sound. BACKGROUND: Patients with primary FSGS unresponsive to current immunosuppressive drugs have few therapeutic options and a poor prognosis. The FONT II Phase II study is an NIDDK funded trial (DK70341) designed to test novel antifibrotic agents as renoprotective therapy in participants age 1-50 with FSGS resistant to steroids and to at least one other standard immunosuppressive drug. Eligibility criteria include central biopsy review and confirmation of primary FSGS OR documentation of a genetic mutation in a podocyte protein associated with the disease, urine protein:creatinine ratio >1 in a first morning sample, GFRe >40 ml/min/1.73 m², no evidence of liver, cardiac, GI or hematological disease, and absence of serious infection. The original design was to compare standard conservative therapy (SCT) consisting of lisinopril, losartan, and lipitor versus SCT plus adalimumab versus SCT plus rosiglitazone. The Treatment Period is 6 months. The primary endpoint of the study is a 50% reduction in proteinuria with stabilization of the GFRe. RESULTS: There are 14 sites in the FONT II network. There are currently 7 patients enrolled in the study. Because of promising preclinical data and patient interest, galactose was added as a fourth arm. However, in response to the ongoing controversy about cardiovascular safety surrounding the use of rosiglitazone, it was dropped from the study. The projected sample size is 137 patients (42 to the SCT and adalimumab arms and 53 to the galactose arm). A 2-step statistical analysis will expedite identification of ineffective therapies. A website - www.fonttrial.org - has been set up for interested patients and physicians.

ADDING COHORT FOLLOW UP TO THE END OF A RANDOMIZED TRIAL
Jennifer Gassman, Susan Sherer, Brett Larive, Mary Pipkin, Gerald Beck and the FHN Trial Group
Cleveland Clinic, Cleveland, OH, USA

When a trial’s treatment interventions and data collection end, investigators often question what will happen next in the clinical course of their patients, especially in trials where interventions end shortly before data collection ends and investigators expect significant results. Researchers want to know if expected treatment benefits will continue after the trial.

The NIDDK-sponsored Frequent Hemodialysis Network (FHN) Daily and Nocturnal Trials randomized patients to 3x/week vs 6x/week dialysis at their dialysis units (Daily Trial, NEJM online 11/20/2010) or to 3x/week vs 6 nights/week at home (Nocturnal Trial). Investigators wondered whether expected treatment benefits would continue after the trial and whether patients preferring 6x/week would be able to continue that regimen.

The FHN Trial Group obtained funding for extra follow up including study coordinator effort. The additional time permitted extra biorepository sample collection and data collection on patient dialysis regimens and major events.

For the extension, the DCC needed to create a reasonable data collection system that was doable by minimally funded coordinators and palatable to patients who might be burned out from the demands of the trial. The DCC and the study leadership also needed to balance meeting the curiosity of investigators who wanted to continue collecting data at the intensity of the trial protocol and meeting study coordinator time limitations. Each site needed new IRB approval and consent forms and most needed new subcontracts. Obtaining subcontracts took longer than anticipated.

Selection bias must be minimized in order for a cohort extension to be valuable. Thus far, study coordinators (who had good relationships with their patients) have been able to obtain cohort follow up consent from most of their patients.
The extended study coordinator funding also allowed for extra data clean up for FHN Trial analyses. The cohort follow up will end in early 2011.

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IMPLEMENTATION OF CARDIOVASCULAR CELL THERAPY CLINICAL TRIALS; POINTS TO CONSIDER
Erica Anderson, Robert Lindblad, Shelly Carter, Nilay Shah, Adam Mendizabal
The EMMES Corporation, Rockville, MD, USA

Cardiovascular stem cell therapy clinical trials have many unique characteristics including varying patient populations and disease indications, varying cell types and sources, varying routes of administration and the interplay between these components. Specific issues include enrollment contingencies, using autologous products, shipping of the cell product, linking manufacturing to participant outcomes, standardizing imaging methods and procedures. Enrollment contingency plans due to failed autologous cell processing should be clearly outlined in the clinical protocol. An expected percentage of participants will never receive the study product because of the study product failing to meet release criteria. Enrollment and randomization should be flexible to account for the unexpected contingencies and to allow replacement of participants that do not receive study product. Product identification, labeling and administration is noted in the CMC section of the IND and linking that product and manufacturing data with the clinical data is critical to assess participant outcomes. Prior to participant accrual, shipping validation must be performed for cell therapy products produced centrally and distributed to multiple sites. Standardization of cardiac imaging (CT / MRI) is important to determine that the make/model of the scanners across all participating centers can obtain comparable images. Development of a centralized reading core is recommended to minimize intra-observer variability. Mechanisms should be employed to record, distribute and track the images for timely reading and analyses with SOPs developed to document the process. Cardiac stem cell therapy clinical trials are increasing in numbers with encouraging signs of safety and efficacy. While studies can be very complex in nature, it is the responsibility of the data coordinating center/research organization to develop standards to ensure consistent implementation of procedures within and across centers.

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LA RED: THE FORMATION OF AN EMERGING INFECTIOUS DISEASES CLINICAL RESEARCH NETWORK IN MEXICO
Guillermo Ruiz-Palacios, M. Lourdes Guerrero, Arturo Galindo-Fraga, Francisco Flores, Alejandra Ramírez, Simón Kawa, Rafael Valdéz, Pedro Gutierrez, Beatriz Llamosas, Onofre Muñoz Sarbelo, Sarbelio Moreno, Evan Stewart, John Beigel, Jorge Tavel
Mexico Emerging Infectious Diseases Clinical Research Network, Mexico City, Mexico

Following the 2009 outbreak of influenza A pandemic (H1N1), the governments of Mexico and the United States of America initiated a partnership to develop clinical research capacity in Mexico, both in order to characterize the then-ongoing epidemic and to provide an infrastructure for use in future public health emergencies. The result of that collaboration, the Mexico Emerging Infectious Diseases Clinical Research Network (“La Red”), unites five hospitals in Mexico City in pursuit of high quality clinical trials: Federico Gómez Children’s Hospital of Mexico, Dr. Manuel Gea Gonzalez General Hospital, National Institute of Pediatrics, National Institute of Respiratory Diseases, and Salvador Zubirán National Institute of Medical Sciences and Nutrition. Network objectives include the creation of an efficient collaborative clinical research network, the dissemination and application of knowledge from infectious disease research, and an exchange of scientists, materials, and information between the two nations. With support from the Mexican Ministry of Health and the U.S. National Institutes of Health, the network has created a governing structure including representatives from the five hospitals involved, trained study personnel at each site in Good Clinical Practices, and created a repository for specimens. La Red’s first trial is an observational study of influenza-like illness which, as of November, had enrolled 291 patients across four sites. Subsequent studies may involve other infectious diseases. Both Mexico and the U.S. recognize that the continued success of La Red will play an important role in ensuring that the two nations are prepared to act cooperatively during future pandemics.
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ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) HOME BLOOD PRESSURE STUDY RESULTS
Annie Green Howard1, William C. Cushman2, Richard H. Grimm3, Jeffrey A. Cutler5, Therese S. Geraci2, Brenda Kirpach3, Peter A. Senior4, Karen L. Margolis3, Jan N. Basile6, Gregory W. Evans1
1Wake Forest University School of Medicine, Winston-Salem, NC, USA; 2Memphis VAMC, Memphis, TN, USA; 3Berman Center for Outcomes & Clinical Research, Minneapolis, MN, USA; 4University of Alberta, Edmonton, Alberta, Canada; 5National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD, USA; 6Medical University of South Carolina, Charleston, SC, USA

The multicenter, randomized ACCORD blood pressure (BP) trial investigated whether treating systolic pressure (SBP) to an intensive goal (<120 mm Hg) reduced major cardiovascular events compared to a standard goal (<140 mm Hg) in 4733 high risk type 2 diabetics followed for an average of 4.7 years. Beyond the first year, mean clinic BP measured using an OMRON HEM-907 averaged 119/64 mm Hg on 3.4 medications for intensive participants and 134/70 mm Hg on 2.1 medications for standard participants. As previously reported, event rates were not significantly reduced for the primary outcome, a composite of fatal and nonfatal major cardiovascular events, but a 41% reduction in stroke, a pre-specified secondary outcome, did achieve nominal significance (p<0.05). To investigate whether between group BP differences were similar outside the clinic environment, we invited ACCORD participants from 8 clinics to enroll in a Home BP ancillary study shortly before their close-out examinations (March-June, 2009). Each participant was asked to record BP twice daily for 3 consecutive days using an Omron HEM- 790IT in their home. Of 231 participants contacted before their close-out examination, 143 (41 intensive and 102 standard) consented. Average BPs were significantly higher at home than in the clinic (intensive: 123/72 mm Hg home vs. 116/59 mm Hg clinic; standard: 138/79 mm Hg home vs. 131/66 mm Hg clinic, p<0.05 in all cases). However, between group differences in average SBP in clinic (mean difference=15.7 mm Hg, 95% CI 12.0-19.4) were similar to those at home (mean difference=15.3 mm Hg, 95% CI 10.6-20.0). Comparable results were obtained for diastolic BPs. Thus, BP differences between intervention groups did appear to be similar at home compared with the clinic, at least during daytime hours. Higher home readings, despite use of similar automated manometers, could result from better adherence and/or technique with the clinic measurements.

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DEVELOPMENT AND IMPLEMENTATION OF THE HIERARCHICAL BAYESIAN DESIGN IN CLINICAL TRIALS WITH MULTIPLE DISEASE TYPES
Qian Shi, Rui Qin, Charles Erlichman, Daniel J. Sargent
Mayo Clinic, Rochester MN, USA

Enhanced knowledge of the biologic and genetic basis of disease is re-defining target populations for new therapeutic agents. Specifically for example in oncology, the potential target indications for a new agent often include various solid tumors and hematologic malignancies that share common signaling pathways. Historically, separate clinical trials of the same agent in populations defined by anatomic site have been proposed and conducted in parallel, with no formal mechanism to share information across tumor types. We developed a Hierarchical Bayesian Design (HBD) to test novel agents in multiple disease settings simultaneously in a single clinical trial. The hierarchical Bayesian design maintains the scientific study integrity in each disease site while allowing for borrowing strength (information) across disease sites when evaluating the treatment effect and toxicities if these outcomes are similar across disease sites. A unified protocol for testing the same agent in multiple disease settings allows greatly improved efficiency in logistics and reduced cost. We have developed statistical algorithms, computer programs and set-up procedures for the hierarchical Bayesian design. The assessment of the study operative characteristics of HBD versus traditional phase II design (testing one regimen on multiple tumor types separately) through an ongoing trial (NCT01010126) of testing temsirolimus and bevacizumab in five tumor groups: endometrial, ovarian, hepatocellular carcinoma, carcinoid and islet cell cancer is ongoing.
A TOXICITY-ADAPTIVE ISOTONIC DESIGN FOR COMBINATION THERAPY IN ONCOLOGY
Rui Qin, Paul Haluska
Mayo Clinic Rochester, MN, USA

With the development of molecularly targeted drugs in cancer treatment, combination therapy targeting multiple pathways to achieve potential synergy becomes increasingly popular. While the dosing range of individual drug may be defined, the maximum tolerated dose of combination therapy is yet to be determined in a new phase I trial. The possible dose level combination which are partially ordered poses a great challenge for conventional dose-finding designs. We have proposed to estimate toxicity probability by isotonic regression and incorporate the attribution of toxicity into the consideration of dose escalation and de-escalation of combination therapy. Simulation studies are conducted to understand and assess its operational characteristics under various scenarios. The application of this novel design into an ongoing phase I clinical trial with dual agents is further illustrated as an example.

CLINICALLY SIGNIFICANT EFFECT SIZES FOR SURVIVAL AND RESPONSE ENDPOINTS USING THE 1/2 STANDARD DEVIATION RULE
Amylou C. Dueck, Paul J. Novotny, Daniel J. Sargent,
Paul A. Decker, Randolph S. Marks, Heidi Nelson, Jeff A. Sloan
Mayo Clinic, Scottsdale, AZ, USA

Background: Clinically significant effect sizes have been the focus of much research for assessing patient-reported outcomes. Methods such as the empirical rule effect size (ERES) or ½ standard deviation (SD) method are useful for efficient design and improved interpretation of clinical studies. While the concept of clinical significance is ubiquitous in PRO research, it is less standardized in clinical trials involving tumor response and survival endpoints.

Methods: We applied the ½ SD rule to survival and response endpoints in order to define clinically significant effect sizes for these types of studies. We present clinically significant effect sizes for expected mean and median survival based on the exponential distribution and response rate based on the binomial distribution. We demonstrate the method with application to published studies as well as a recently published review of randomized clinical trials.

Results: The clinically significant effect size for survival endpoints is equivalent to 50% of the expected mean survival or roughly 72% of the expected median survival. A small effect size (½ SD) is equivalent to 20% or roughly 29% of the expected mean or median survival, respectively. The clinically significant effect size for response endpoints is a function of the expected response rate. For an expected response rate of 50%, the clinically significant effect size is 25% and a small effect size (½ SD) is 10%.

Conclusions: This method allows for more ready interpretation of the clinical significance of survival and response studies. It allows for direct cross study comparison even if the endpoints are different. It also facilitates study design as it builds clinical significance into the study directly.
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USING THE HECKMAN MODEL TO IMPUTE INDIRECT FINANCIAL BURDEN FOR THE SURGICAL TREATMENTS OUTCOMES PROJECT FOR DYSFUNCTIONAL UTERINE BLEEDING (STOP-DUB) TRIAL
Lynn Huynh, Kevin Frick
Johns Hopkins Bloomberg School of Public Health Baltimore, MD, USA

Objective: To examine the distribution of health care expenditure by source of payment and to estimate the financial burden the women bear in the Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Trial. Method: The financial burden that the women with dysfunctional uterine bleeding bear is comprised of two parts - the direct charges from the hospital billing records and the productivity costs from missed days of work. From the Trial, we have the direct charges from the completed follow-up visits after surgery. To supplement the Trial data to obtain the productivity cost from the societal perspective, we used data from the Current Population Survey (CPS) from January 1998 to January 2002. To analyze data from the CPS, we introduce the Heckman method to predict the salary and earnings of women in the CPS with a similar distribution of marital status, age, education and insurance as the women in the Trial. We selected to use the Heckman model because it corrects for non-randomly selected samples. To calculate the salary and earnings, these women were selected from a subpopulation who worked which introduces a selection bias. The Heckman model corrects for this selection bias in two steps. In the first step, we use a probit model to estimate the probability of working. In the second step, we correct for the self-selection by including the probability of working into the model with the explanatory variables such as marital status, age, education, and insurance. Results: Table 1 provides the direct charges from the hospital billing records. The analysis for the productivity cost is in progress. Discussion: Our approach to supplement the Trial data using CPS to calculate the productivity cost will allow us to calculate the overall direct and indirect financial burden of surgical treatments for women experiencing dysfunctional uterine bleeding.

P107
PREDICTORS OF BLOOD PRESSURE CONTROL AT 6 AND 12 MONTHS IN THE SECONDARY PREVENTION OF SMALL SUBCORTICAL STROKES (SPS3) STUDY
Lindsey N. Hornung1, Jeff M. Szychowski1, Carole L. White2, John W. Graves3, Pablo E. Pergola2, Leslie A. McClure1, Christopher Coffey4, Robert G. Hart2, Oscar R. Benavente5
1University of Alabama at Birmingham, Birmingham, AL, USA; 2University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; 3Mayo Clinic, Rochester, MN, USA; 4University of Iowa, Iowa City, IA, USA; 5University of British Columbia, Vancouver, British Columbia, Canada

Background: Although there is a clear association between hypertension and stroke, successful control of systolic blood pressure (SBP) post-stroke is still suboptimal. The aim of these analyses was to identify clinical risk factors and patient characteristics that can be used to predict SBP control in hypertensive patients.

Methods: SPS3 is a multicenter, multinational clinical trial with sites in the United States, Canada, Spain, and Latin America. Patients with prior subcortical stroke are randomized to usual (130-149 mmHg) and intensive (<130 mmHg) SBP target groups, and to antiplatelet therapy for prevention of recurrent stroke. SBP is monitored at quarterly follow-ups allowing for continued management. We consider n=545 usual and n=519 intensive patients in logistic regression models examining individual predictors of SBP control at the 6 and 12 month visits. Significant factors identified in univariate models were included in multivariable models.

Results: After multiple covariate adjustment, successful SBP control at 3 months was associated with control at 6 months (OR, 95% CI = 1.96, 1.45-2.66), while missing a scheduled visit (0.64, 0.48-0.86) and baseline SBP (0.88, 0.80-0.97 per 10mmHg) were negatively associated with control. Among participants in the intensive group, use of diuretics was associated with increased control (2.87, 1.84-4.48). Findings were similar for the 12-month visit with the exception that patients from US sites were less likely controlled (0.69, 0.51-0.93) at 12 months compared to patients from all other sites.

Conclusions: These results suggest greater difficulties achieving SBP control among US patients, and also illustrate that higher SBP and missing scheduled clinic visits impede control. Patients in control early in the trial also tend to be controlled later in the trial. These findings should be considered in the planning of future clinical trials of SBP control.
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