VOLUME 36, #2 NEWSLETTER FEBRUARY 2025

INSIDE THIS ISSUE:

SCT President's Column

Dear Friends and Colleagues,

Scott R. Evans, PhD
Society for Clinical Trials President 2024-2025

I hope that you all have had a winter season and are looking forward to the spring. Our thoughts are with our friends in the greater Los Angeles area whom have suffered from the fires. We also wish a speedy return to our government colleagues at the NIH, FDA, CDC, and other agencies, so that that they can continue their important contributions to activities in the broader clinical trial community.

Clinical trials are the most important medical invention in history. They are without equal in providing the most robust information regarding the benefits and harms of interventions for treating and preventing human disease. We share a duty in protecting the ideals and principles that make the clinical trial the pinnacle of evidence, and in reminding the world of their unparalleled value. I look forward to the annual meeting where we continue to perform this important duty together.

In the "A Dose of Clinical Trials Education and History" section of this newsletter issue, I provide a primer on composite endpoints, the challenges and opportunities that they pose, and stories of DSMB case studies that involved composite outcomes. In the "A Historical Clinical Trial" section, I describe the impact of the landmark Systolic Blood Pressure Intervention Trial (SPRINT). In "An Intervention to Watch in Clinical Trials", I discuss the growing interest in phage treatment for serious bacterial infections that are highly resistant to antibiotics, including an interesting case study. Looking forward to the annual SCT meeting in May, I discuss Stanley Park in "A Glimpse into Vancouver".

Scott R. Evans, PhD
President, Society for Clinical Trials

By Colin Begg,
Editor

February 2025 Issue Highlights

The **February** issue of ***Clinical Trials*** contains articles covering the broad range of interests of our readers. On the methodological front, **Ted Karrison, Chen Hu** and **Jim Dignam** examine problems in using restricted mean survival time as a measure of treatment effectiveness, offering some suggestions. **Aryelly Rodriguez** and colleagues address the challenges of effectively anonymizing datasets to facilitate data sharing. **Andrew Vickers** and colleagues describe their experiences conducting large pragmatic surgery clinical trials and the steps they took to facilitate recruitment and follow-up. **Guangyu Tong** and colleagues address the issue of small numbers of clusters in stepped-wedge cluster trials and the corresponding methodological challenges that this presents. On the ethics front, **Emily Largent** and colleagues address the issues surrounding pragmatic clinical trials conducted with waivers of informed consent. Finally, on the policy front, **Gregory Vaughan, Roger Du** and **Fred Ledley** address the impact of the Inflation Reduction Act on the pipeline of new drug approvals. As always we encourage you all to submit your research findings to ***Clinical Trials***.

Follow the brand new "Society for Clinical Trials" company page on LinkedIn to keep up to date with the latest from the journal!

Membership Spotlight

B. Aletta Sanny Nonyane, PhD MS
Research Professor
Johns Hopkins University

What is your current position?

I am a Statistician and Research Professor in the Department of International Health at the Bloomberg School of Public Health, Johns Hopkins University. My career has primarily focused on international collaborations within multidisciplinary research teams and consortiums working on preventing, diagnosing, and treating TB and HIV. I have been the primary statistician on several individual- and cluster-randomized clinical trials and implementation science studies with funding from various sources, including the NIH, USAID, CDC, PCORI, and Bill and Melinda Gates Foundation. The studies have included HIV PrEP implementation, TB case-finding, strategies for linking communities to HIV and TB services, scaling up TB preventive therapy, evaluating the safety of co-administrating TB and HIV drugs, as well as evaluating shorter regiments for TB. Through the TB and HIV consortiums, I provide statistical guidance on the design and analyses of studies to colleagues, and postdoctoral and doctoral trainees at Johns Hopkins University and abroad.

What are your past positions?

- 10/2010–09/2023
  Assistant Scientist, Associate Scientist, Senior Scientist, Bloomberg School of Public Health, Johns Hopkins University
- 06/2008–05/2010
  Research Fellow**,** London School of Hygiene and Tropical Medicine, UK
- 01/2006–05/2008
  Post-Doctoral Fellow, School of Public Health and Health Sciences, University of Massachusetts, Amherst
- 03/2004–10/2005
  Research Fellow, University of Birmingham, Department of Primary Care

What is your training?

PhD Statistics; MSc Statistics; MSc Finance (Economic Policy).

What are your specific research interests or your specific interests within clinical trials?

Methodology

a. Design and analysis of individual- and cluster-randomized trials.
b. Analysis of longitudinal healthcare data.
c. Applying novel methods to designing and analyzing clinical trials, as well as drawing inference using data sources that are not specifically designed for research purposes.

Public health applications

a. Evaluating approaches for improving access to services for TB and HIV diagnosis and care.
b. HIV prevention among adolescent girls and young women, TB prevention and treatment among children and adults.

What are your hobbies (outside of work)?

a. Fitness training
b. Traveling
c. Fashion (vintage fashion!) and beauty

What role(s) did/do you play in SCT?

- Membership Committee member

What is your favorite part about being involved in clinical trials?

- Guiding the statistical design and data analysis plans.
- Primary outcomes analyses.
- It is an honor and privilege to contribute to knowledge that informs how we can prevent disease and provide care to those who are affected.

  - **Your least favorite?**
    - Disruptions to the study design and/or implementation plans. Having to replace participants or sites post-randomization makes me nervous!
    - Relying on institutions outside our study team for clinical trial data. This is increasingly becoming the norm because of the nature of the implementation science studies where we collaborate with national programs on TB and HIV to evaluate their implementation strategies. Novel statistical methods are needed to make inference using data sources that are not specifically designed for research purposes.

What do you enjoy most about attending the SCT Annual Meeting? And/or:

I attended the SCT Annual Meeting for the first time in 2023. I enjoyed the various themes covered in the talks and posters. I also had an opportunity to network with fellow statisticians and others in the field of clinical trials. The 2024 meeting was also very informative and I organized a roundtable discussion on implementation of complex clinical trials.

How has being in SCT benefited you?

- Sharing ideas with those outside the teams that I collaborate with.
- Improving my leadership skills through being part of the membership committee

What advice would you have for junior researchers just starting out in the field of clinical trials?

- Regular data monitoring during study implementation is crucial!
- Overcome the fear and ask questions so you can learn.
- Be in the meeting room, the dinner party, or the golf course where important professional connections can potentially be made.

What is one strategy you have used to maintain your sanity during the recent months/years?

- Early morning walks!
- Take a break from watching the news. Even our local gym has stopped showing national news on their screens ☺

SOCIETY FOR CLINICAL TRIALS

Registration for SCT's 2025 Annual Meeting is now open!

Please join us! This year's theme is:

"Shaping the Future: The Right Questions, Robust Answers"

May 18 - 21, 2025

Hyatt Regency Vancouver

Vancouver, British Columbia, Canada

Our Annual Meeting brings together the clinical trials community from academia, the pharmaceutical and device industries, government agencies, medical groups, and clinical research entities.

Click here to learn more about SCT's 2025 Annual Meeting and to register.

Highlights include:

- Cutting-edge pre-conference workshops by leaders in the field
- Invited sessions, targeted sessions, contributed sessions, and poster presentations
- Curtis Meinert Keynote Lecture delivered by Dr. Arun Sanyal
- Founders Lecture
- Annual Thomas C. Chalmers Student Scholarship competition
- Sylvan Green Award presentation by Dr. Ryan Berry
- Exhibitors showcasing publications, technology innovators, and other resources for clinical trials
- Discussions of timely issues and research experiences among colleagues in the field
- Presentation of the SCT Class of 2025 Fellows
- Presentation of the 2024 David Sackett Trial of the Year Award
- Roundtable small group discussions on a wide range of topics
- Networking with your colleagues

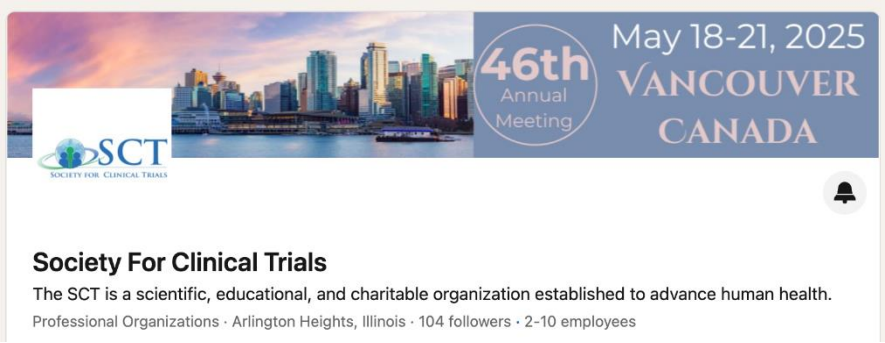
We're looking forward to seeing you this May in Vancouver. **REGISTER TODAY**

Need to contact us? Registration: registration@sctweb.org **General Inquiries:** contact@sctweb.org

The Brand New SCT LinkedIn Company Page Is Now Public!

SCT LinkedIn Page Now Public!

The Society for Clinical Trials has launched a new **public** LinkedIn page! Previously, SCT's presence on LinkedIn was limited to a private members-only group, but now everyone can follow our page to stay informed about clinical trial methodologies, upcoming events, educational opportunities, and more.



We encourage all members of the previous private group to transition to this new page, as we will be closing the old group in a few months. Follow and share our page to stay connected and help expand awareness of clinical trials.

Follow us here: [https://www.linkedin.com/company/society-for-clinical-trials/]

The SCT 2025 Member Volunteer Portal is open! Submit your interest by June 13, 2025.

Our volunteers are the heart of the Society and your skills, talents, and perspectives are needed to enable us to continue to build a strong, energetic, and dynamic organization.

If you are interested in serving on a committee, we encourage you to share your interest through the Member Volunteer Portal.

Committee Chairs, Co-Chairs, and Past Chairs serve one-year terms. Committee Members have the ability to serve up to five years.

To submit your interest, please follow the steps below:

- Go to **http://www.sctweb.org/**.
- Log into the **Members-Only Area** with your username and password.
- Navigate to the right of your screen and click on **Member Volunteer Portal.**
- Follow the prompts in the portal and please be sure to indicate which committee(s) you're interested in serving on.
- Please download the Conflicts of Interest document, disclose your financial and other relationships in accordance with the SCT Conflict of Interest (COI) Policy, and upload the completed form through the portal.

Please note the volunteer portal will close on Friday, June 13th (11:59 pm CT).

If you have need any assistance with your SCT login, please email membership@sctweb.org.

If you have any general questions, please email contact@sctweb.org.

Thank you for your continued support of the Society for Clinical Trials!

Join SCT for our next educational webinar

It Takes a Village: Multi-Disciplinary Approach to Designing Stellar Data Collection Forms

March 18, 2025 | 3:00- 4:00 pm ET

We invite you to participate in our upcoming webinar that will focus on the form development process from the perspective of a collection of stakeholders. This webinar is free to SCT members and non-members.

Session Overview:

As is often best recognized in hindsight, the design and content of data collection forms can make or break a clinical trial. During early stages of form development, it is critical to have all parties involved and engaged. From determining what questions to ask, how best to code answers and integrating branching logic, inclusion of investigators, project managers, programmers, biostatisticians, and clinical site staff is crucial every step of the way.

This webinar will take attendees through the forms development process from start to finish, highlighting the perspectives of each of these key stakeholders: investigators, project managers, biostatisticians, programmers and clinic coordinators. Items to be addressed will include: translating trial protocol eligibility, adherence and outcome information into a targeted and concise form; assessing participant burden; understandability to the end user; data validation; developing a form matrix; form versioning; discussion of paper versus electronic forms; staff vs. participant data entry; and evaluating each final form version to assure feasibility of all protocol-specified analyses.

This webinar will give participants an opportunity to expand their understanding of the different design considerations and consequences for form development. The team of presenters represent a cross-section of all disciplines and will demonstrate how this multi-disciplinary approach can work within a typical clinical trial. This model has been successfully implemented in many multi-site projects around the world, including refinement of best practices after receiving and integrating suggestions from clinical staff throughout the globe.

By the end of this webinar, participants should be able to:

1. Understand the importance of including all stakeholders at the beginning of the form development process.
2. Identify how the flow and wording of data collection forms can impact the data collection.
3. Discuss the pros and cons of a variety of data collection methods.

Moderator: Gustavo Jimenez-Maggiora, PhD, MBA, BS, Director of Informatics and Data Management, University of Southern California

Presenters:

- Emily Dressler, PhD, Professor and Interim Chair, Department of Biostatistics and Data Science, Wake Forest University School of Medicine
- Letitia H. Perdue, MS, Senior Manager of Clinical Research, Department of Biostatistics and Data Science, Wake Forest University School of Medicine
- Laura Lovato, MS, Biostatistician, Department of Biostatistics and Data Science, Wake Forest University School of Medicine
- Mark King, Lead Programmer/Analyst, Department of Biostatistics and Data Science, Wake Forest University School of Medicine
- Lindsay Tysinger, Project Manager, Department of Gerontology, Wake Forest University School of Medicine

REGISTER NOW

A Dose of Clinical Trials Education and History

By Dr. Scott R. Evans

Scientific Topics in Clinical Trials: Composite Outcomes

Composite outcomes such as (i) major adverse cardiovascular events (MACE) e.g., stroke, myocardial infarction, and death in cardiovascular disease, and (ii) progression free survival (PFS) i.e., avoidance of cancer progression and death in oncology, are common endpoints in clinical trials. Composite endpoints may provide a more complete characterization of patient status where the cumulative nature of events on individual participants can be observed and described, can help deal with competing risks e.g., death through the incorporation of such competing events, and can reduce the required sample size when estimating relative risk though clinical importance should drive the decision for inclusion rather than sample size.

Interpretation of composites is challenging when: (i) the relative importance of components of the composite differs e.g., death being more important than other components as with MACE, or clinical components (death) being more important than surrogates (progression) as with PFS, (ii) the treatment effects for different components go in opposing directions or vary greatly in magnitude, or (iii) components of lesser importance are more prevalent and dominate statistics associated with the result. Significance on a composite does not imply significance on the components, nor does significance on the components imply significance on the composite.

It is advised to de-composing composite outcomes and report data on all components to reveal and understand the full story. Comprehensive understanding requires careful evaluation the relative importance of the components, which components are driving the observed effects on the composite, and whether the effects on the components go in similar vs. opposing directions. Continued follow-up of trial participants that experience an event is advised to determine if multiple events occur and evaluate future survival status. Former SCT president Jim Neaton has beautiful paper about these issues in the *Journal of Cardiac Failure*!

Composite endpoints are inherently patient-centric and pragmatic. During the design of clinical trials, several endpoints or outcomes on trial participants are specified. Typically, efficacy and safety outcomes are evaluated in silos, one outcome at a time. The primary endpoint is analyzed; results in treatment A are aggregated, results in treatment B are aggregated, and then treatments are compared. This process is repeated for all of the other endpoints. Benefit:risk analyses is sometimes conducted by combining the separate marginal analyses together in some way. Unfortunately, this standard approach does not compose data in a manner consistent with the way the outcomes are experience by patients. It fails to incorporate associations between or the cumulative nature of multiple outcomes in individual patients, suffers from competing risk complexities during interpretation of individual outcomes, fails to recognize important gradations of patient-centric responses, and since efficacy and safety analyses are often conducted on different populations, benefit:risk generalizability is unclear. Treatment effect heterogeneity is typically evaluated based on a single efficacy or safety endpoint and rarely evaluated based on patient-centric benefit:risk.

Suppose a person is diagnosed with a serious disease. Treatment is being selected among three treatment options, A, B, and C. A trial comparing these alternatives is conducted. There are two major outcomes, considered equally important: (i) treatment success, a binary efficacy variable, and (ii) a binary safety event. There were 100 patients in each arm. There was a 50% treatment success rate in A, 50% in B and 50% in C. The safety event rate was 30% in A, 50% in B and 50% in C. Which treatment do you choose?

	Treatment		
	A (N=100)	**B (N=100)**	**C (N=100)**
Treatment Success	50 (50%)	50 (50%)	50 (50%)
Safety Event	30 (30%)	50 (50%)	50 (50%)

They all have the same success rate, and A has the lowest safety rate. B and C are indistinguishable. Clearly A should be chosen.

This represent the typical analyze one outcome at a time approach. Patients are randomized, followed over time

and used to analyze the outcomes. However suppose that this strategy is inverted, instead "using the outcomes to analyze the patients rather than patients to analyze the outcomes". Quoting Sir William Osler, one of the founders of Johns Hopkins Hospital, "The good physician treats the disease; the great physician treats the patient who has the disease."

There are four possible "patient outcomes". A patient may experience treatment success with or without the safety event, or they may not experience treatment success with or without the safety event. Treatment success and safety outcomes can be composed within patient to examine the distribution of the patient outcomes by treatment arm.

	Treatment		
	A (N=100)	**B (N=100)**	**C (N=100)**
Treatment Success; No Safety Event	35 (35%)	0 (0%)	50 (50%)
Treatment Success; Safety Event	15 (15%)	50 (50%)	0 (0%)
No Treatment Success; Safety Event	15 (15%)	0 (0%)	50 (50%)
No Treatment Success; No Safety Event	35 (35%)	50 (50%)	0 (0%)

In treatment A, there was no correlation between the success and the safety event, resulting in 35 patients that experienced the treatment success and avoided the safety problem. In treatment B, the outcomes were positively correlated resulting in zero patients with success without the safety event. In treatment C, the outcomes were negatively correlated resulting in 50 patients that experienced success and avoided the safety event. This is striking since the typical analyses was unable to distinguish between treatments B and C though they are importantly different. Since treatment success and the safety event have similar importance, nobody assigned to treatment B had a net benefit. In contrast, treatment C may be a good treatment if the right subgroup of patients for its application can be identified. Typical analyses combining marginal effects are blind to this difference. Quoting Aristotle "The whole is greater than the sum of its parts." Perhaps we need to check our usual clinical trial arithmetic.

Critical thought is needed regarding how to aggregate data to describe treatment effects on patients and better inform medical decision-making. One important lesson is that not all composites have to be binary. The MACE and PFS composite endpoints described above essentially count all components the same. If importantly different then it makes sense to recognize the differential importance when creating the composite endpoint. For example, PFS composes mortality and progression, treating them equally. However, mortality is more important than progression. A more layered endpoint recognizing this distinction could be constructed. For example a three-level ordinal endpoint: (i) alive without progression (most desirable); (ii) alive with progression; and (iii) death (least desirable) could be constructed based on the concept of desirability, representing a closer reflection of the overall patient-response. MACE endpoints compose e.g., mortality, stroke and myocardial infarction (MI), treating them equally. A finer gradation of the composition could be constructed to recognize that mortality is more important than non-fatal events, more events is worse than fewer events, and that events with permanent/disable sequelae are worse than transient/non-disabling sequelae. For example, a five-level ordinal endpoint based on desirability: (i) alive with no events (most desirable); (ii) alive with one transient/non-disabling event; (iii) alive with more than one transient/non-disabling event; (iv) alive with one permanent/disabling event; and (v) death (least desirable), recognizes important gradations of patient response. Robust analyses of such endpoints may provide more useful information to inform clinical practice.

The purpose of measuring the outcomes in the trial is to inform patient status particularly in late phase trials where there is a focus on describing and making inferences regarding the disease burden and impact on patients. Composite endpoints are part of the solution. They create challenges but with careful forethought, such challenges can be overcome.

A Historical Clinical Trial: Systolic Blood Pressure Intervention Trial (SPRINT)

The landmark Systolic Blood Pressure Intervention Trial (SPRINT) trial was motivated by findings from the Global Burden of Disease study (GBD). The GBD identified elevated blood pressure as the leading risk factor, among 67 studied, for death and disability-adjusted life-years lost during 2010. Furthermore, hypertension was highly prevalent in adults in the United States, especially among people over sixty years of age.

Clinical trials had shown that treatment of hypertension reduces the risk of cardiovascular disease outcomes, including incident stroke by 35-40%, myocardial infarction by 15-25%, and heart failure by up to 64%. However, the target for systolic blood pressure lowering was uncertain. Observational studies had shown a progressive increase in cardiovascular risk as systolic blood pressure rises above 115 mm Hg, however evidence from clinical trials was lacking for targets less than 150 mm Hg.

The SPRINT trial randomized 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary outcome was a composite time to event where events included myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary outcome in the intensive-treatment group than in the standard-treatment group (hazard ratio and 95% confidence interval of 0.75 (0.64 to 0.89); P<0.001). Examining the five components of the composite, heart failure (38% lower relative risk) and death from cardiovascular causes (43% lower relative risk) were significantly reduced, while all other components had point estimates for hazard ratios of 1.0 or less. Furthermore all-cause mortality was significantly lower in the intensive-treatment group (hazard ratio, 0.73 (0.60 to 0.90); P = 0.003). The trial also noted increased rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, with intensive-treatment.

The SPRINT clinical trial added important evidence of the benefits of lowering systolic blood pressure to lower target levels than had been previously recommended in most patients with hypertension, especially in older patients. SPRINT demonstrated that aggressively lowering systolic blood pressure to less than 120 mmHg, compared to the standard target of less than 140 mmHg, results in a reduction in cardiovascular events and all-cause mortality in high-risk patients without diabetes. The results led to updated clinical guidelines recommending more intensive blood pressure control for certain individuals. Concerns remained about the potential side effects such as hypotension and the generalizability of the findings to diverse populations. This highlights to the importance of proper application in clinical practice requires through accurate assessment of blood pressure and reliable evidence of high cardiovascular risk.

DSMB Stories: HOPE, COMET-ICE, and the Complexities of Composites

DSMBs must consider the results of composite endpoints carefully during interim evaluation of clinical trials utilizing composite endpoints. Even if a formal evaluation of the composite outcome crosses a boundary, more data may be needed to fully understand the effects and confirm the consistency and stability of emerging trends.

HOPE

The Heart Outcomes Prevention Evaluation (HOPE) clinical trial was a randomized double-blinded factorial trial comparing Ramipril vs. placebo and vitamin E vs. placebo in patients at high-risk for cardiovascular outcomes. 9,541 patients from 267 centers in 19 countries were randomized. The primary outcome was the time to MI, stroke, or cardiovascular death. Important secondary outcomes included heart failure and renal progression.

The boundary for the primary endpoint was crossed during the fourth interim analyses. This triggered detailed examination of the totality of evidence to evaluate if additional data were needed to fully understand the effects. The consistency of the treatment effect on each component of the composite and secondary outcomes was examined and confirmed. The treatment effect was evaluated in important subgroups. There was no indication of important treatment effect heterogeneity. The DSMB requested repeating the analyses after an additional four months of follow-up to ensure that the results were not episodic fluctuations. Subsequent analyses confirmed result stability. The DSMB then recommended termination of the trial.

COMET–ICE

The Covid-19 Monoclonal antibody Efficacy Trial-Intent to Care Early (COMET-ICE) was a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, in non-hospitalized patients with symptomatic Covid-19 and at least one risk factor for disease progression (33). Beginning in October 2020, trial participants were randomized (1:1) to an intravenous infusion of sotrovimab 500 mg (a pan-sarbecovirus monoclonal antibody) or placebo. The primary endpoint was Covid-19 progression, defined as hospitalization longer than 24 hours or death for any cause, through day 29.

On March 10, 2021, the DSMB reviewed interim data. Primary efficacy outcome data were available for 583 randomized participants (291 sotrovimab vs. 292 placebo). COVID-19 progression was observed in 21 (7%) of participants randomized to placebo vs. 3 (1%) randomized to sotrovimab, resulting in an 85% RR reduction 97.24% CI = (44%, 96%), p=0.002, meeting statistical criteria for trial termination for efficacy. The magnitude of the effect was substantive and unlikely due to chance. Should the DSMB recommend stopping the trial?

The DSMB navigated the composite nature of the primary outcome consisting of (i) hospitalization longer than 24 hours and (ii) death. Death is more important than hospitalization. It would be difficult to interpret a scenario whereby placebo had higher rate of Covid-19 progression but with all of the events being hospitalization whereas the sotrovimab arm had lower rates of progression but all events were deaths. Fortunately, this was not the case with only a single death observed, and that was in the placebo arm. Thus, results were primarily driven by the hospitalization component. The DSMB considered whether trial continuation would provide substantively more information on the most important component of mortality. This was deemed unlikely given only one observed death and the remaining targeted enrollment. What about important secondary outcomes and safety? Are more data needed to thoroughly understand the benefit:risk profile? Does equipoise still exist to support continued randomization and ethical assignment to placebo?

The DSMB conducted further detailed evaluation to understand the result and compare the implications of recommended trial continuation vs. early termination. Other efficacy endpoint results favored sotrovimab consistent with the primary endpoint. Safety concerns were not identified and some safety outcomes favored sotrovimab. After evaluating these issues and considering the current Covid-19 treatment landscape with no approved and available alternative treatments, the DSMB recommended cessation of trial enrollment on March 10, 2021, when 1057 patients of the planned 1360 had been randomized (13).

An Intervention to Watch in Clinical Trials: Phage

In November of 2015, a married couple, Tom Patterson, a psychologist, and Steffanie Strathdee, a world-renowned epidemiologist, were taking a vacation in Egypt. During the trip, Dr. Patterson came down with a stomach ailment. He began antibiotic treatment for his illness and was expected to improve. Instead, however, his condition deteriorated.

Dr. Robert Schooley, a friend and Chief of Infectious Diseases at UC San Diego where the couple worked, advised them to have Dr. Patterson admitted to a hospital or clinic in Egypt. After several tests and procedures, the physicians at the clinic realized that Dr. Patterson's condition was very serious. Patterson was transferred to a German hospital noted for infectious diseases research.

At the German hospital, Dr. Stefan Zeuzem, a colleague of Dr. Schooley, found Patterson to have an acute case of pancreatitis and a pseudocyst in his abdomen caused by a gallstone. Endoscopic surgery was performed to further investigate the problem. They found that the pseudocyst had been there long before the couple went on vacation. Analysis of the fluid in the pseudocyst found an infection due to *Acinetobacter baumannii* (*A baumannii*), considered to be the one of the worst bacteria (superbug) on the planet by the World Health Organization. More than 3,000 American and European soldiers and military contractors who served in Iraq developed *A baumannii* infections.

Patterson was flown to the UC Medical Center in San Diego for further treatment. At first, the antibiotics seemed to work. However, eventually the *A baumannii* became resistant to the all of the available antibiotics! Bacteria such as *A baumannii* can develop resistance to antibiotics through a microorganism version of Darwinian evolution.

Patterson's wife refused to give up. She began researching alternative cures for *A baumannii* infections. These included phage therapy. Phage therapy utilizes bacteriophages, viruses that target and kill bacteria but are believed to be relatively benign to the patient. Bacteriophage therapy has been around since

the 1930's, however their use in treating patients in the Western world was largely abandoned with the emergence of effective antibiotics such as penicillin in the mid-1900's. Bacteriophage have attractive features including bactericidal activity, specificity for target pathogens including *A baumannii*, amplification in vivo in the presence of target bacteria, avoidance of host tissue damage, preservation of the human microbiome in comparison to antibiotics, and synergy with antibiotics. However, rigorous scientific investigations including controlled clinical trials have yet to evaluate the utility of bacteriophage therapy to treat bacterial infections in clinical practice.

Patterson's wife Dr. Strathdee contacted Dr. Schooley and posed the idea of treating her husband with phage therapy. Dr. Schooley thought it was a good idea, but noted that it would probably only be allowed for "compassionate use" a regulatory term meaning that the patient could be treated with a yet unproven experimental therapy if they were likely to die without such therapy.

A major challenge with the application of phage therapy is to find the right virus or combination of viruses that are equipped and tailored to attack and kill the specific superbug that the patient has. There is an estimated 10^{31} phages on the planet.

Unfortunately, there were very few phage centers across the globe and most of them were located overseas in Eastern Europe in the Republic of Georgia, Poland and Russia. Nonetheless, Patterson's team began the process of finding a phage or mixture of phages that might save his life. Meanwhile, Patterson's condition deteriorated and he lapsed into a coma. The search for an effective phage cocktail took many twists and turns and seemed to work for a while, but improvements were transient.
After much experimentation, a two-stage therapy was begun four months after Patterson became ill. After eight weeks, the treatment was finally successful. They never learned what triggered the gallstone pancreatitis or the pseudocyst nor would they ever know where Patterson contacted *A. baumannii.*

Case reports like Dr. Patterson's story, describing positive outcomes resulting from bacteriophage treatment of complex infections, has created interest in
revisiting bacteriophage as a treatment option in difficult to treat infections. Controlled clinical trials of phage therapy are now being conducted. For example, the Antibacterial Resistance Leadership Group (ARLG) funded by the NIAID/NIH is conducting a randomized phase trial in adult cystic fibrosis volunteers with *Pseudomonas aeruginosa* airway colonization, another highly antibiotic-resistant superbug. Many questions about dosing and frequency, how to manufacture and tailor phage, how to do susceptibility testing, and how to use in combination with antibiotics are being evaluated.

Covariate Adjustment in Randomized Clinical Trials: New Methods and Applications

The **17th Annual Conference on Statistical Issues in Clinical Trials** will be held on **April 7, 2025** in the Rubenstein Auditorium & Commons at the Perelman School of Medicine's Smilow Center for Translational Research (3400 Civic Center Boulevard, Philadelphia, PA).

While baseline characteristics tend to be balanced in a randomized clinical trial, adjusting for prognostic covariates can improve the statistical power to detect treatment effects. Although this principle is well known, questions about how to effectively and validly implement covariate adjustment are an area of active biostatistical research. Our speakers will cover topics of broad relevance to the field, as well as more specific work related to covariate adjustment in group-sequential and re-randomization designs, complexities of adjustment in the face of missing covariate data, machine-learning for covariate selection and the role of covariate adjustment in the drug and device approval process.

The conference includes morning and afternoon panel discussions along with time for audience participation. This is a hybrid conference offering in-person and virtual options. In-person registration includes breakfast and lunch with multiple opportunities for networking.

Registration is Now Open!

This year's topic is Covariate Adjustment in Randomized Clinical Trials: New Methods and Applications. Our Keynote Speaker is Stuart Pocock, Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine. As in past years, one can attend in person or virtually.

DEPARTMENT of BIOSTATISTICS EPIDEMIOLOGY & INFORMATICS | Perelman SCHOOL OF MEDICINE University of Pennsylvania

Conference information and registration link: https://web.cvent.com/event/e36f0626-b91b-4575-8b8e-0f00fcc17765/summary

Early Bird registration closes March 7!

This is a hybrid event. There is limited capacity available for in-person registration. If you unable to register for in-person attendance, please pick one of the available virtual options.

IMPACT-AD 2025 REQUEST FOR APPLICATIONS

February 3, 2025 – With support from the National Institute on Aging and the Alzheimer's Association, a program to train the next generation of clinical trialists in Alzheimer's Disease and Related Dementias (ADRD) will be offered **August 24 – August 29, 2025,** in **San Diego**, CA. The Institute on **M**ethods and **P**rotocols for the **A**dvancement of **C**linical **T**rials in **AD**RD (IMPACT-AD) provides a unique, comprehensive, and active learning experience in AD/ADRD trials by leveraging the full infrastructure and expertise of the Alzheimer's Clinical Trials Consortium (ACTC). IMPACT-AD is open to a diverse range of clinicians, scientists and research professionals including those with and without previous experience in AD/ADRD. IMPACT-AD provides modern and robust training on AD/ADRD clinical trials by experienced and renowned clinical trialists with a focus on team science. Training topics include AD/ADRD trial design, biostatistics, participant recruitment and retention, trial ethics, outcome measures (clinical, imaging, digital and biofluid biomarkers), study management and more.

IMPACT-AD 2025 is now accepting applications. Individuals with broad ranging experience and expertise in AD/ADRD and/or clinical trials with an interest in a career in AD/ADRD clinical trials are encouraged to apply. IMPACT-AD will cover all travel costs for accepted trainees.

Two unique in-person tracks will be offered as part of IMPACT-AD 2025. Tracks will commence simultaneously and overlap. They include the:

- **Professionals Track** - This track seeks applications from individuals with at least 2 years of experience in AD/ADRD research and/or clinical trials who wish to further their knowledge and advance their careers in AD/ADRD clinical trials. Applicants may currently serve in a broad variety of roles including, but not limited to clinicians, study coordinators, statisticians, psychometricians, and other study professionals (3.5 days).
- **Fellowship Track** - This track seeks applications from individuals seeking to serve as Principal Investigators in AD/ADRD trials now or in the future and offers mentored training in protocol development. Applications are open to individuals in their fellowship or postdoctoral training, faculty members or equivalent positions (5 days).

Participation is competitive and open to individuals with a full-time position at their respective institution within the United States. Please read the eligibility criteria for each track carefully and ensure your qualifications align appropriately. Applicants are permitted to apply to **only one track** per application cycle.

Application Submission requirements:

- NIH Biosketch (both tracks)
- A career statement (both tracks)
- Institutional letter of support (both tracks)
- Brief trial synopsis (Fellowship track only)

All materials must be submitted electronically through ProposalCentral **by 5:00PM PST April 30, 2025**. Attendees will be selected after expert peer review of application materials and notified the first week of June 2025. Priority will be given to applicants whose career statement, institutional letter of support, and (if applicable) the quality of the proposed research synopsis (significance, innovation, and approach), demonstrate a commitment to AD/ADRD clinical trials research.

Participation in the Global Pilot Program: If your place of residence and primary appointment are outside of the United States, you might be eligible for our global pilot program. If interested, please email your CV/Biosketch and a Letter of Support to our IMPACT-AD Program Email Address, and include "IMPACT-AD 2025 Global Eligibility" in the subject of your email. Your materials will be reviewed, and you will be notified regarding your eligibility to apply. Please do not submit an application to ProposalCentral unless your eligibility has been reviewed via this mechanism. If you do not receive a response within a week, please resend your materials.

More information, including submission templates and instructions, an informational webinar and a FAQ, is available at the IMPACT-AD website (www.impact-ad.org). For other questions, please contact the IMPACT-AD Program Administrator, Ms. Maggie Mastrolorenzo, or submit a question to our program email.

Women in Statistics and Data Science | conference

November 12–14, 2025 • Cincinnati, Ohio

Join an Extraordinary Group of Professionals and Students This November

Seeking inspiration, knowledge, and community? The **2025 Women in Statistics and Data Science** conference in **Cincinnati, Ohio**, is going to be an epic event you don't want to miss. Mark your calendars for **November 12–14**.

WSDS unites a dynamic, diverse, and accomplished group of individuals and is a celebration of the voices, perspectives, and power of women shaping the future of the profession. The infectious energy and passion of this community make it an experience like no other.

What You Can Look Forward To

- **Exciting technical talks highlighting groundbreaking and innovative research**
- **Inspiring plenary sessions that will leave you revitalized**
- **Casual networking opportunities to connect, collaborate, and ignite innovative ideas**

WSDS 2025 Website

Important Dates

Participate

March 31 – May 15: Concurrent, Panel, and Poster Session Abstract Submission

Attend

June 30: Early Registration Opens

WSDS 2025 Host Hotel

WSDS 2025

Cincinnati, Ohio | November 12–14

Hilton Cincinnati Netherland Plaza

Save the date!

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The Data Coordinating Center (DCC) is a component of the Clinical Trials Program in the Department of Biostatistics and Medical Informatics at the UW School of Medicine and Public Health. The DCC supports investigator-initiated NIH or industry-sponsored RCTs. We provide expertise in planning, conduct, monitoring, and analysis of clinical trials.

Bronze Sponsor

STATACORP

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Future SCT Meetings

Save the Dates - Upcoming SCT Annual Meetings

46th Annual Meeting
May 18-21, 2025
Vancouver, BC

47th Annual Meeting
May 17-20, 2026
Phoenix, AZ

48th Annual Meeting
May 16-19, 2027
Chicago, IL

A Glimpse into Vancouver: Stanley Park

Vancouver's Stanley Park is a large, beautiful, popular park that is easily accessible. It is 10% larger than Central Park in New York. One can bike ride or walk along the famous Seawall, enjoying scenic views of water, mountains, sky, and forest. There are many gardens, monuments, wildlife, and trails for walking. The Park is home to the Hollow Tree, the remnants of a stump from a western red cedar tree that is about 60 feet in circumference and a popular spot for photos. It is home to the 9 o'clock gun, a cannon that is ordinarily fired daily at 9:00 pm. Stanley Park is named after Governor General Lord Frederick Stanley… as is the Stanley Cup championship trophy awarded annually to the National Hockey League (NHL) playoff champion.