SOCIETY FOR CLINICAL TRIALS

VOLUME 36, #1 NEWSLETTER NOVEMBER 2024

INSIDE THIS ISSUE:

SCT President's Column

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

Dear Friends and Colleagues,

I hope that you all have had a great summer.

Thank you to everyone that participated in the annual meeting in Boston in May. The meeting was a terrific success and it was great to see long-time friends and meet new ones. Thank you to President Dixie Ecklund for her thoughtful leadership and to the Board and Committee members for their important contributions that helped to create an educational, productive, and enjoyable meeting. The meeting demonstrated the strong recovery and reinvigorated health of the Society after the unfortunate trough created by the COVID pandemic. We look forward to another great meeting in 2025 in Vancouver.

There are changes to the newsletter, decreased frequency and enhanced content. New content includes a section entitled "A Dose of Clinical Trials Education and History". The section may tell the story of a historical clinical trial, the story of a DSMB experience with an important moral, or a brief educational summary on important scientific topics or operational issues in clinical trials. In this issue, I provide a primer on surrogate endpoints, as well as the story of a historical trial in the treatment of diabetes and a DSMB case study that involved surrogates.

In the Future SCT Meetings section of the newsletter, I share the motivation for the 2025 meeting theme: "Shaping the Future: The Right Questions, Robust Answers", and present a brief glimpse into Vancouver in preparation for the 2025 annual meeting.

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

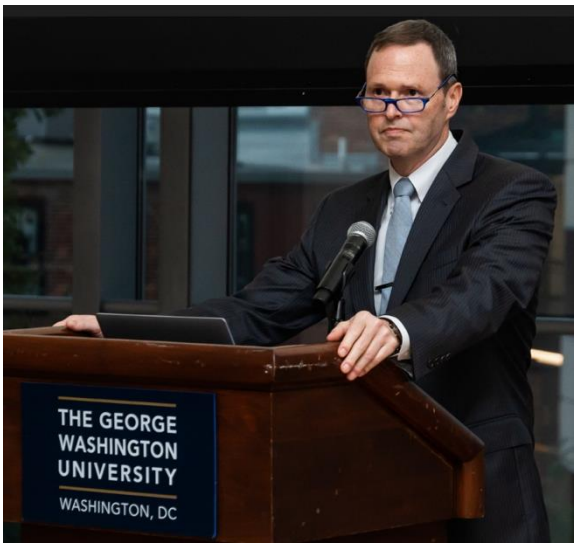
October 2024 Issue Highlights

By Colin Begg, Editor

The **October** issue of ***Clinical Trials*** features many articles addressing time to event analyses of clinical trials, from reports of talks presented at the 15th University of Pennsylvania Conference on Clinical Trials, organized by **Mary Putt**. In other articles in the issue **Laura Levit** and colleagues examine the ethics of requiring research biopsies for clinical research studies, highlighting the incentive structure that encourages collection of biopsies and the need to fully justify the secondary research aims that motivate them. **Anna Kearney** and colleagues review the literature on recruitment and retention methodology, pointing out that these issues are frequently investigated separately though the issues are closely linked. In a point-counterpoint exchange of opinions **Michael Fay** and **Fan Li** discuss the absence of a straightforward causal interpretation of the hazard ratio in clinical trials but argue for its continued use as a key estimand, while **Dan Heitjan** advocates a countervailing opinion.

Join the Society for Clinical Trials group on LinkedIn to keep up to date with the latest from the journal!

Membership Spotlight



Scott R. Evans, PhD, MS
Director, Biostatistics Center
Professor and Founding Chair, Department of Biostatistics and Bioinformatics

What is your current position?

I am the Director of The Biostatistics Center and a Professor and Founding Chair of the Department of Biostatistics and Bioinformatics at Milken Institute School of Public Health of the George Washington University (GWU). The Biostatistics Center, the largest research Center at the GWU, celebrated this year its 51st year of leadership in practice-changing clinical trials, biostatistical methodology research, and the education of students and researchers. I am the principal investigator for grants from the NIAID/NIH, NCI/NIH, and the NHLBI/NIH. I teach Principles of Clinical Trials and Advanced Topics in Clinical Trials with my friend and colleague Professor Toshi Hamasaki.

What are your past positions?

I was in the Harvard School of Public Health for more than 18 years. I taught the same courses, Principles of Clinical

Trials and Advanced Topics in Clinical Trials, and had grants from NIAID/NIH, NINDS/NIH, and NIMH/NIH. About five years ago I moved to GWU. Luckily my research team of faculty and staff moved with me. The uprooting of their families was quite a disruption and sacrifice. We stimulated the economy with the selling of houses in Boston and the buying of houses in greater DC.

What is your training?
I have a PhD in Biostatistics and an MS in Mathematics.

What are your specific research interests or your specific interests within clinical trials?
One area of focus is the development of desirability of outcome ranking (DOOR), a paradigm for the design, data monitoring, analysis, interpretation, and reporting of clinical trials based on patient-centric benefit-risk evaluation. The concept is to use outcomes to analyze patients rather than patients to analyze outcomes, creating more pragmatic answers by addressing the most important "real world" question to aid clinical decision-making: how do resulting patient experiences, when comprehensively considering benefits and harms, compare between therapeutic alternatives? Other interests include DSMB issues, and benefit-risk evaluation of diagnostics. We have about ten doctoral students working on methods related to these initiatives.
I am interested in all disease areas though have focused recently on bacterial infections and antibiotic resistance. I also work in oncology, cardiovascular disease, aging, neurology, diabetes, and maternal-fetal medicine.

I have great interest in clinical trials education to ensure maintenance of a broad appreciation of clinical trials as the evidentiary standard, and ensure that clinical trials retain the rigors (objectivity, analytical error control, robust / model and assumption free) that are foundational for clinical trials serving as the robust pinnacle of evidence. Seemingly more than ever we see researchers pressured to move away from clinical trials in favor of observational evidence, and researchers implementing approaches that are concessions of robustness, compromising the evidentiary standard, though camouflaged in labels of innovation.

What are your hobbies (outside of work)?

Recently it has been entertaining my two new kids, ages 80 and 81 … named "Mom" and "Dad", who recently moved in with me. It is hard raising parents these days but I enjoy having them around. I like to exercise and the outdoors.

What role(s) did/do you play in SCT?
I am the President and serve on the Executive Committee and the Nominating Committee. I am active with the SCT DMC Training Initiative.

I was on the Board of Directors from 2014 to 2018. I served on the David Sackett Trial of the Year Committee from 2015 to 2019, chairing the last four years. I served on several committees including the Program Committee, Development Committee, Nominating Committee, Strategic Plan Oversight Task Force, and as a representative to the CTTI Steering Committee.

I have taught a few short courses and have been a presenter and organizer at several annual meetings.

What is your favorite part about being involved in clinical trials?
I enjoy the feeling of advancing knowledge that helps people, and advancing methods that help researchers do better research. I like working with and appreciate others that feel this same enjoyment.

- **Your least favorite?**
  Probably my least favorite is being distracted from the fun and constructive scientific thinking to address e.g., compliance, operating procedure, or documentation issues. Sometimes I feel like I spend one hour a day answering doodle polls, another hour a day looking for or changing passwords, and the rest of the day wasting time!

What do you enjoy most about attending the SCT Annual Meeting? And/or:
The things that I enjoy most are seeing old friends and meeting new ones. Last year I particularly enjoyed watching our (seven) doctoral students give presentations. It is rewarding to see the next generation grow.

How has being in SCT benefited you?
The annual meeting was an opportunity, early in my career, to interact with some of my clinical trial role models such as Dave DeMets, Janet Wittes, Susan Ellenberg, John Lachin, and Jim Neaton. I am fortunate to still interact with them. Dave, Susan and I work on DMC

issues together, Janet gives a guest lecture in my course, and I work with John at the Biostatistics Center. Over the years I was able to learn from the meeting sessions and short courses and eventually give back by transitioning from the back to the front of the room. I see the SCT as having an important role in the development of students and staff.

I have long appreciated the SCT journal which has a unique niche publishing papers on various issues in the science and operation of clinical trials. Our department at Harvard hard-bounded all of the issues from the birth of the journal. When the department converted to a mostly electronic library, they gave me the complete set of the hard bound issues. I still have them in my office.

I hope that the society can educate regarding and reaffirm the importance of clinical trials as the source of the most replicable and trusted evidence, and re-store and protect the rigor in trials that provides for it place on the mountain top of trustworthy evidence. The world has slipped a bit in these areas.

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

- Work hard at finding the question before searching for answers.
- Place increased interest on questions of a pragmatic origin. These are the most important questions for patients and clinicians.
- Find opportunities for others.
- Pretend to be the best person you can imagine; you will become that person. (I borrowed this one from David Sackett.)
- Be motivated to do things better rather than faster than cheaper.
- When sacrifice is necessary, and sometimes it is, sacrifice quantity based on feasibility while protecting quality. Otherwise, we will be unable to fully understand the evidence.
- Do not rush your answers.
- Ask a lot of questions before answering one.
- Think about a problem, develop your own ideas for solutions, before researching how others have approached it. This is how novel thinking begins.
- Protect scientific integrity. Clinical trials are our strongest tool.
- Educate others regarding clinical trial concepts and sound approaches.
- It is better to know how to learn than to know. Go beyond what, into why.
- Keep educating yourself. Science does not stand still.
- Know the medical literature. Interpret it critically.
- Learn to distinguish innovations advancing science vs. compromises advertised as such. It is better to walk alone than in a crowd in the wrong direction.
- Develop effective communication skills (listening, writing, speaking, and presenting). Tailor to your audience. Learn to explain complicated things in simple ways.
- Educate colleagues about what you do and learn from them about what they do.
- Be proactive.
- Identify options and their pros and cons. Strive for objectivity.
- Avoid being isolated.
- Be an inquisitive detective.
- Voice scientific opinions. Ensure they are well-rationalized.
- Find mentors. Use your references and resources.
- Own and learn from your mistakes.
- Finish the job.
- Participate in professional societies, attend professional meetings, and take short courses. Participate in SCT!

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

A good data manager would justifiably query the premise of your question. It assumes facts not in evidence! A few things seem to help: saving a little time to spend with my closest friends, talking with my parents, spending time away from the computer with exercise in fresh air, and focusing on helping others facing the same challenges.

SCT's 2025 Annual Meeting Submission Portal is Still Open!

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

May 18-21, 2025
Hyatt Regency Vancouver
Vancouver, British Columbia, Canada

All submissions must be made via the SCT website.

Roundtable Topic Submissions
Submission Deadline: November 1, 2024, by 11:59 pm ET
Roundtables are informal conversations on a variety of topics such as "Career Paths in Clinical Trials" that will take place during lunch at the Annual Meeting. If you'd like to share your knowledge in an interesting roundtable discussion, we invite you to **submit a proposed topic**.

Thomas C. Chalmers Student Scholarship Applications
Submission Deadline: November 15, 2024, by 11:59 pm ET
Are you a graduate student or post-doctoral fellow interested in sharing your knowledge on clinical trials? If so, we encourage you to **submit an application** for the Thomas C. Chalmers Student Scholarship. The top three selected finalists will each give an oral presentation at the Annual Meeting.

Sylvan Green Award Applications
Submission Deadline: November 15, 2024, by 11:59 pm ET
Are you a physician, dentist, or other health professional interested in sharing your work on clinical trials? If so, we urge you to **submit an application** for the Sylvan Green Award. The selected recipient will give an oral presentation at the Annual Meeting.

SCT 2025 Fellow Nominations
Submission Deadline: November 15, 2024, by 11:59 pm ET
Nominations for the 2025 Fellows are currently being accepted and any member of the Society may nominate a candidate. Complete nomination packets are due by November 15, 2024. The Class of 2025 Fellows will be announced and honored at the SCT 46th Annual Meeting.

Contributed (Oral/Poster) Proposals
Submission Deadline: November 22, 2024, by 11:59 pm ET
If you're interested in sharing novel research on the design, organization, operations, analysis, ethics, or reporting of clinical trials, we invite you to **submit a proposal** for consideration as an oral/poster presentation.

ED&I Early-Career Award Application
Submission Deadline: November 22, 2024, by 11:59 pm ET
We welcome applicants involved in any aspect of clinical trials methodology, development, conduct or dissemination including but not limited to ethics, information systems/data management, and patient advocacy to name a few. We encourage all who are interested in the ED&I Early-Career Award to **submit their application online**.

All content entered in the submission portal by the designated deadlines will be considered final.
No extensions will be given.

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Visit the SCT website for more information.

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A Dose of Clinical Trials Education and History

By Dr. Scott R. Evans

Surrogate Endpoints

A surrogate outcome is a measure that is predictive of a clinical outcome but takes a shorter time to observe or is less expensive or less invasive to measure. Analysis of the ideal surrogate endpoint would result in the same conclusions if the clinical endpoint were used. Surrogates have been invaluable in clinical trials evaluating interventions for many disease areas. Examples include viral load in HIV or HbA1C in diabetes.

However surrogacy is a high bar. Many measurements that are believed to be surrogates turn out not to show surrogacy when attempts are made to validate them. Significant correlation does not necessarily imply that a marker is an appropriate surrogate.

For example, in oncology, progression-free survival is commonly utilized as an endpoint in clinical trials because physicians often consider it a surrogate for prolonged survival or improved quality of life. However, recent studies have indicated that many cancer drugs that have been granted accelerated approval did not demonstrate benefit in overall survival or quality of life within 5 years of accelerated approval.

In 2007, the NEJM published an open-label Eastern Cooperative Oncology Group (ECOG) study comparing paclitaxel to paclitaxel plus Avastin for first-line treatment of metastatic breast cancer. The Avastin arm had prolonged PFS (11.8 vs. 5.9 mos., HR = 0.60, $P < 0.001$). Median survival, however, was similar in the two groups (26.7 vs. 25.2 mos.). No differences were seen in quality of life. After considerable discussion with their advisory committee, the FDA granted accelerated approval to Avastin.

With accelerated approval, the FDA required additional studies to validate surrogacy through the evaluation of clinical effects. In July 2010, the FDA Advisory Committee reviewed two additional studies, AVADO and RIBBON-1. Neither study showed large differences in PFS, overall survival was not improved, and the Avastin group experienced significantly more severe adverse events. In December 2010, the FDA withdrew approval for the breast cancer indication for Avastin, since the required post-marketing studies after accelerated approval based on a surrogate endpoint did not indicate a survival or quality of life benefit, and increased toxicity risk.

The BELLINI trial, a randomized, double-blind, placebo-controlled trial of venetoclax vs. placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma, resulted in significant improvement in PFS with venetoclax but also increased mortality mostly because of an increased rate of infections. The venetoclax arm showed longer PFS (22.4 vs. 11.5 months), response rate (82% vs 68%), and minimal residual disease negative rates (13.4% vs. 1%). However, the venetoclax arm had higher mortality 41/194 (21.1%) than placebo 11/97 (11.3%), HR 2.03 (1.04-3.94).

The concerns that commonly used endpoints are not appropriate surrogates is not limited to oncology. Tredaptive is a drug that increases HDL (good) cholesterol in patients at risk for heart disease with low HDL. It was approved in 70 countries including the European Union in 2008 based on trials that showed significant increases in HDL. Tredaptive was not approved by the FDA, which wished to see a clinical outcome trial rather than relying on HDL as a surrogate.

The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial was a 4-year trial with 26,000 participants. It compared statin + Tredaptive vs. statin alone with the endpoint being the time-to-heart attack or coronary death, stroke, or need for arterial bypass. Tredaptive again clearly raised HCL but did not result in clinical benefits. It also increased severe adverse events and new onset diabetes.

Other recent studies have shown that most surrogate markers used as primary end points in clinical trials to support FDA approval of drugs treating nononcologic chronic diseases, lacked high-strength evidence of associations with clinical outcomes from published meta-analyses.

Care must be taken when interpreting surrogate outcomes. Clinical outcomes are most important and it may be necessary to continue trials to evaluate clinical outcomes.

A Historical Clinical Trial: The Diabetes Control and Complications Trial (DCCT)

Since the discovery of insulin in 1921, the medical community debated whether elevation of blood glucose (hyperglycemia) associated with diabetes mellitus was responsible for the development and progression of the microvascular complications of type 1 diabetes (T1D) or insulin-dependent diabetes such as retinopathy leading to blindness, nephropathy leading to end-stage kidney disease, cardiovascular disease including stroke and myocardial infarction, and neuropathy leading to loss of sensation, ulceration and amputation. Would treatment that normalizes glucose levels lowering HbA1c, prevent or delay these long-term complications?

The Diabetes Control and Complications Trial (DCCT: 1982-1994) involved 28 clinical centers and five laboratories, tested the glucose hypothesis, a theory that elevated blood glucose associated with diabetes was responsible for the development and progression of diabetes complications. 1441 patients, consisting of 726 with no retinopathy (primary prevention cohort) and 715 with mild retinopathy (secondary prevention cohort) were recruited from 1983-1989. Participants randomized to intensive therapy (monitoring) versus standard of care (control). The primary outcome was the appearance or progression of retinopathy.

Early on, the DCCT DSMB observed worsening of microaneurysms on the intensive treatment arm in the secondary prevention cohort. There was concern that this "surrogate" was the beginning of visual acuity decline. However, the DSMB waited to see if changes in the primary outcome of retinopathy and other clinical effects would emerge. The intuition, wisdom, and patience of the DSMB later paid off. Later, the DSMB stopped the trial for clear evidence of efficacy of the intensive therapy, reducing microvascular complications by 26-63% over a mean follow-up of 6.5 years. The results established glycemia as a major risk factor and mechanism for the onset of T1D complications, and set a new worldwide standard for T1D care.

The DCCT led to therapeutic interventions that drastically reduced diabetes-related blindness, renal failure and amputation, from 30%, 35%, and 12% pre-DCCT to 1%, 1%, and 1% post-DCCT, respectively. The DCCT spurred development of a clinical guidelines by the American Diabetes Association (ADA), spurred creation of the National Diabetes Education Program to disseminate the findings to the public (www.ndep.nih.gov), stimulated research efforts to develop tools and therapies that aid patients in achieving control of blood glucose levels, and incentivized many states to provide mandatory coverage of supplies for intensive therapy.

The primary publication for the DCCT has been cited more than 27,000 times, the most frequent citation in the diabetes treatment literature. The Harvard Health Letter named the DCCT the most significant advancement in medicine in 1993, "because it asked important questions, was carried out with great care, and generated clear-cut answers. Its results will help millions of people with diabetes live longer and healthier lives." The DCCT Research Group was awarded the Charles H. Best Medal in 1994 by the American Diabetes Association for "Distinguished Service in the Cause of Diabetes."

DCCT Follow-up: Epidemiology of Diabetes Interventions and Complications (EDIC) Study

The average age of DCCT study participants was 34 years old at end of the study. There was a desire to understand the effects of diabetes treatment on long-term macrovascular disease and severe microvascular complications. The EDIC began in 1996 as a multi-center, longitudinal, observational study designed to utilize the well-characterized DCCT cohort.

The long-term benefits of reductions in glycemia during the treatment have been profound, a phenomenon termed metabolic memory. There is still an approximate 50% reduction in the following outcomes in the intensive therapy group compared with control group: severe retinopathy, need for laser eye surgery, vision loss; foot ulcers; renal failure; amputations; and cardiovascular disease. These discoveries have to date resulted in more than 376 publications including 9 in the *New England Journal of Medicine*.

The follow-up of the DCCT cohort through the EDIC continues, now in year 41, the longest and most impactful study of T1D and its complications in history. Today 87% of the surviving cohort continues to be followed with an average follow-up of 38 years. Studies are examining the interface between T1D and aging now that people with T1D are living near normal life spans, owing in part to use of intensive therapy pioneered by the DCCT. The cohort closely resembles the US population, with 35% overweight and 40% obese, providing the opportunity to evaluate the impact of obesity on the progression of

diabetes- and aging-related outcomes.

A DSMB Story

Protecting the welfare of participants in clinical trials through the monitoring of trial results is an ethical imperative. Trials are ethical when there is uncertainty regarding the relative benefits and risks of interventions under study. It would be unethical to randomly assign patients to an intervention known to be inferior to a therapeutic alternative. Furthermore, it would be shameful to wait until trial completion to discover that an intervention was unacceptably harmful or had unparalleled benefits, when that discovery could have been made earlier and appropriate action could have been taken to ensure that participants received the appropriate treatment.

The data and safety monitoring board (DSMB) was conceived for this purpose. A DSMB is a small group that reviews accumulating clinical trial data by treatment group in order to monitor patient outcomes, ensure the validity and integrity of the trial, and make a benefit/risk assessment. The DSMB enhances the scientific integrity of the clinical trial, as it is the only entity with access to aggregate trial data by unblinded treatment assignment, which is required for comprehensive understanding of emerging treatment effects, whether beneficial or harmful. This allows trial sponsors and study staff to remain blinded to ongoing trial results, protecting the integrity of the clinical trial.

The DSMB has an extremely challenging job. Stop a trial too soon, and the trial is inconclusive and fails to obtain answers to important questions that inform clinical practice. Stop a trial too late, and participants are exposed to potentially harmful or ineffective interventions, which can be either the novel treatment or the current standard of care, longer than necessary. The benefits of obtaining convincing and conclusive evidence and the ethical responsibility to current and future patients are weighed carefully during DSMB deliberations.

The Cardiac Arrhythmia Suppression Trial (CAST) and the Assumptions of Surrogacy

The Cardiac Arrhythmia Suppression Trial (CAST), a randomized placebo-controlled trial sponsored by the NHLBI, evaluated the effects of encainide, flecainide, and moricizine, which at the time of the trial were FDA-approved drugs for the treatment of cardiac arrhythmias, on the incidence of sudden cardiac death or all-cause death in patients after a myocardial infarction (MI). The belief in the early 1980s was that cardiac arrhythmia increased the risk of sudden or cardiovascular death, and thus treatment with antiarrhythmic drugs to suppress arrhythmias would reduce cardiac death.

CAST was designed to randomly assign 4400 patients to encainide, flecainide, moricizine, or placebo which provided 90% power to detect a 30% decrease in sudden death using a one-tailed 0.05 significance level. A pre–randomized assignment run-in period identified patients with a sufficient response, defined by 80% arrhythmia suppression to one of the drugs, for trial entry. The primary endpoint was sudden cardiac death; total mortality was a secondary endpoint. CAST began enrollment in 1987.

Two years later, the DSMB recommended discontinuation of the encainide and flecainide arms as a result of increased mortality. In the encainide and flecainide arms there were 33 sudden cardiac deaths on treatment and nine on placebo. There were 56 total deaths on the encainide and flecainide arms and 22 on placebo. Two years after that, the DSMB recommended discontinuation of the moricizine arm for similar reasons. The trial was terminated after observing only 15% of the planned events due to dramatic increases in sudden death and total mortality.

The CAST DSMB story demonstrates the challenges of surrogate endpoints and the necessity to validate them. Prior to the CAST trial, the consensus was that suppression of asymptomatic or minimally symptomatic ventricular arrhythmias was beneficial in patients surviving an MI. Since arrhythmias are correlated with subsequent risk of sudden death and total morality, we may be tempted to leap to the conclusion that suppression of arrhythmias is a surrogate for the clinical outcomes of sudden death and mortality. CAST is reminder of the dangers of such assumptions.

Clinical Trials Transformation Initiative (CTTI) Activity Updates

SCT representatives to the CTTI Steering Committee:

Dr. Barbara Braffett

Dr. Yves Rosenberg

The Clinical Trials Transformation Initiative (CTTI) held their Fall Member Meeting on September 19th, 2024 in Washington DC. As a reminder, the CTTI is a public-private partnership between the U.S. Food and Drug Administration and Duke University established in 2007 that is working to modernize the clinical trials enterprise to make trials "more streamlined, efficient, and patient-focused." CTTI multiple stakeholders work together to identify and encourage the adoption of practices that will increase the quality and efficiency of clinical trials. The SCT is one of the more than 80 organizations now represented on its Steering Committee. Throughout the meeting, attendees discussed considerations for optimizing master protocols, implementing diversity action plans, and modernizing good clinical practices. Several key themes emerged for advancing innovations supported by recent regulatory guidance and unlocking strategies to bridge the gap between guidance and practice:

- CTTI has also recently launched a new project, Optimizing Data Quality and Flexibility in Clinical Trials, which focuses on ensuring data quality while adopting flexible approaches to clinical trials. By aligning with recent FDA guidance, the project aims to address key challenges and promote the wider use of flexible methods to improve trial outcomes and efficiency.
- In addition, the NIHR Clinical Trials Toolkit has recently integrated CTTI's Quality by Design and Recruitment Planning recommendations, providing even more valuable guidance to trialists worldwide. These updates help improve trial quality, streamline processes, and optimize participant recruitment – offering practical solutions for conducting successful clinical trials.
- Finally, last month, CTTI's Large Simple Trials publication was cited in an FDA-released draft guidance titled "Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice". As part of FDA's Real-World Evidence Program, this guidance is intended to support the conduct of randomized controlled drug trials with streamlined protocols and procedures that focus on essential data collection, allowing integration of research into routine clinical practice.

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Equity, Diversity & Inclusion:
Mitra Lewis (Chair)
Cody Chiuzan (Co-Chair)
Kaleab Abebe (Past Chair)

Education:
Sarah Gaussoin (Chair)
Denise Esserman (Co-Chair)
Gustavo Jimenez-Maggiora (Past Chair)

Fellows:
Anne Lindblad (Chair)
William Meurer (Co-Chair)
Christopher Coffey (Past Chair)

Membership:
Cristina Murray-Krezan (Chair)
Emine Bayman (Co-Chair)
Julie Qidwai (Past Chair)

Nominating:
Sharon Love (Chair)
Lori Dodd (Co-Chair)

Outreach:
Susan Halabi (Chair)
Chen Hu (Co-Chair)
Amarjot Kaur (Past Chair)

Program:
Cory Goldstein (Chair)
Fan Li (Co-Chair)
Charity Patterson (Past Chair)

Student Scholarship:
Farah Khandwala (Chair)
Sumihiro Suzuki (Co-Chair)
Ludovic Trinquart (Past Chair)

Trial of the Year:
Jessica Overbey (Chair)
Jonathan Cook (Co-Chair)
Andrew Cook (Past Chair)

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

President's Message

Impetus and Rationale for the Theme "Shaping the Future: The Right Questions, Robust Answers" for the Society for Clinical Trials' 2025 Annual Meeting

Clinical trialists often evaluate, discuss, and debate how to design, conduct, or analyze a trial. Discussions may involve endpoints, interventions, populations, or analyses. At its core, what is being deliberated is not the answer, but the question. Once the subtleties of the ultimate question are well-defined and understood, the path to the answer becomes clearer. Jonas Salk wrote "What people think of as the moment of discovery … is really the discovery of the question."

A few years ago, I constructed strengths, weaknesses, opportunities, and threats (SWOT) analyses for clinical trials as part of the keynote talk at the Regulatory Industry Statistics Workshop organized the Biopharmaceutical Section of the American Statistical Association. It looked something like this:

- Strengths
  - Randomization (the foundation for statistical inference)
  - Blinding
  - Control groups
  - Prospective observation
  - ITT (protects the benefits of randomization; assesses pragmatic questions)
  - Standardization of measurement and procedures
  - A comprehensive protocol outlining scientific strategy and operational approaches
  - Pre-specification of endpoints and hypotheses providing multiplicity context and a framework by which to control errors and provide the correct coverage probabilities
  - Protection of trial participants and trial integrity via independent monitoring of benefits and harms by DSMBs
  - Registration which increases transparency and helps to curtail selective reporting
- Weaknesses
  - Expensive and resource intensive
  - Time-consuming
  - May lack generalizability and clinical applicability if not pragmatic, for example with use of restrictive entry criteria, surrogate rather than clinical endpoints, per protocol rather than ITT analysis sets, and marginal analyses of endpoints rather than patient-centric evaluation
- Opportunities
  - Greater pragmatism: more relevant questions and answers for clinical practice and decision-making
  - Emerging technologies to timely obtain important data
  - Improving clinical trials education with emphasis on fundamentals of the scientific principles and operations. Clinical trials provide for the pinnacle of clinical evidence. Many that are involved with the trial process have only a surface level understanding of why, or how to protect trial integrity so that trials produce the highest quality evidence.
  - Improvement to DSMB processes. We know how to do it well. Yet poor reporting practices remain prevalent. DSMBs denied access to important e.g., efficacy data. Reports are often voluminous and indigestible with lengthy tables and listings,

void or limited with regard to figures that are more effective at displaying data trends and outliers, and without an executive summary that notes important results. Training for reporting teams and for DSMB members will provide for improved comprehension of the data and ultimate decision-making.

- Threats
  - Innate desire to do things faster and cheaper, magnified by business and political pressures. Though understandable, such desires can threaten objectivity and best decision-making, and result in studies with low replicability, integrity, and applicability.
  - Insufficient education regarding the role of clinical trials as a scientific instrument rather than a commercial tool. A "successful trial" has been perverted to imply a positive trial, rather than a trial that addresses important questions and gets robust answers to those questions regardless of the directionality and magnitude of the treatment effects. In 2019, Tom Fleming delivered the Curtis Meinert Keynote Lecture at the annual meeting of the Society noting that we should be objective about the objective, i.e., striving to correctly "determine whether" an effect exists rather than "to establish" that one does.
  - Misinformation, disinformation, and incomplete information regarding the merits of trending methods and technologies. Some current approaches are labeled as innovative, presented with a degree of commercialism rather than scientific objectivity. But are these innovations progress…or regress? Closer evaluation of approaches reveals that they are fancy ways of lowering the usual integrity and evidentiary standards and introduce greater uncertainty through concessions of: (i) robustness via greater reliance upon assumptions, (ii) objectivity via the incorporation of beliefs, (iii) transparency relenting to black box approaches, and (iv) the theoretical foundation for statistical inference. See efforts to protect the scientific community from compromises in scientific rigor and the decline in integrity in e.g., Emerson and Fleming telling "the rest of the story" and Collins, Bowman, and Landray, and Peto's "The magic of randomization versus the myth of real-world evidence". We share a duty in protecting these ideals in areas where it has abated.
  - A concerning decline of academic leadership in clinical trials. Former SCT president David DeMets and FDA Commissioner Rob Califf wrote "where have the academics gone?" When I arrived at Harvard in 2000, most faculty were engaged in clinical trials. When I left in 2018, very few were engaged in trials. I attributed this to two main reasons: (1) emerging technologies and advances such as the mapping of the human genome created new and interesting statistical challenges and opportunities, and (2) the increasing regulatory hurdles, focus on SOPs and programming validation etc. were turn-offs for academics interested in working on scientific challenges. The clinical trial community is in need of more academic leadership.

Pragmatic "Patient-Centric" Approaches to Clinical Trials

Improving clinical practice and the lives of our fellow mankind is the ultimate goal of the clinical trial community. Randomized clinical trials are the gold standard for evaluating the benefits and harms of interventions, though often fail to provide the evidence to inform medical decision-making. One reason is the failure to recognize the most important questions for treating patients in clinical practice, and using this as the motivation for the design, monitoring, analysis, and reporting of clinical trials. Placing increased interest on questions of a pragmatic origin to match their clinical importance, and adjusting our approaches to address these questions, are a most promising opportunity to greatly advance medicine and public health.

For example, the clinical trial community has been modestly successful with educating its community that the ITT preserves the benefits provided by randomization whereas such benefits would be sacrificed with the exclusion of randomized participants in per protocol (PP) or on-treatment analyses. However we have been less successful at enlightening the community that the ITT analyses, as stated by former SCT president John Lachin "provides the most realistic and unbiased answer to the more relevant question of clinical effectiveness" as a key reason why primary analyses should be conducted according to the ITT principle. Education is critical particularly at this time of mounting pressures to divert from the ITT principle.

Bertrand Russell, the British philosopher and mathematician once said "It's a healthy thing now and

then to hang a question mark on the things you have long taken for granted." The pursuits of pragmatism and "real world" evidence, are noble ones. However these terms are generally defined by the data source. Terms such as "real world" are misleading, seemingly implying that clinical trials that do not use associated data sources do not provide real world evidence. Furthermore, to attain the meaningful goals of pragmatism, obtaining the evidence that is the most useful for informing and guiding clinical practice, requires going beyond the data source. It involves asking the right questions, and implementing methodologies for the design and analyses of trials that are focused on overall effectiveness.

The level applicability of a clinical trial to clinical practice is based on a number of factors. The PRECIS-2 tool highlights eligibility criteria, recruitment methods, trial setting, organization including necessary resources and expertise, flexibility in intervention delivery and adherence, follow-up methodology, the relevancy of outcomes to participants and potential patients, and analyses i.e., inclusion of data from all trial participants. However in order to be optimally pragmatic the outcome must not only be relevant to patients, it must be a holistic assessment of the patient…THE patient outcome… and the analyses must go beyond including all data… it must analyze the patient, rather than siloed elements of the patient.

For example, the standard approach of analyzing one outcome at a time, 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 holistic benefit:risk. Quoting Aristotle, the whole is greater than the sum of its parts. The clinical trials community is so very aware of the concept of repeated measures of a single endpoint on individual patients but generally apathetic to different outcomes on the same patient, despite its inescapable relevance for clinical practice.

Consider metabolic health related disorders. Diet-induced adiposity causes metabolic stress, systemic inflammation and fibrosis. This affects the: arteries (hypertension, CVD, CAD, PVD); heart (HFPEF); liver (NAFDL); pancreas (T2D); kidney (CKD); brain (cognitive decline) and other organs. Yet, despite the shared biology and that these afflictions occurring in the same individual patients, evaluation of treatments is organ-specific. However, the benefits of treatment may be broader, affecting multiple organs, resulting in greater overall benefits to the patient than organ-specific evaluations would uncover.

Thus, an important promising area is "patient-centric" approaches to design, data monitoring, analysis, interpretation, and reporting of trials. Sir William Osler, a Canadian physician and one of the founding professors of Johns Hopkins Hospital said "the good physician treats the disease; the great physician treats the patient who has the disease". There is an important opportunity to strengthen the connection between research and practice by "using the outcomes to analyze the patient rather than the patient to analyze the outcomes".

Strategies as Interventions and the Marriage of Clinical Trials and Diagnostics

Another promising area is evaluation of therapeutic strategies noting that patient management is not based on a single decision. Rather, it is dynamic: based on a sequence of decisions, with therapeutic adjustments made over time. Adjustments are personalized: tailored to individual patients as new information becomes available. However, strategies allowing for such adjustments are infrequently studied. Greater use of sequential multiple assignment randomized trials (SMARTs) can help evaluate such sequential decision-making strategies.

For example, consider the treatment of serious bacterial infections. Here, there are two major decision-points regarding treatment selection: empiric and definitive therapies. Empiric therapy is selected based on the clinicians' best judgment, given the often-limited information that is immediately available upon recognition of the clinical syndrome. Definitive therapy is selected once the organism identification, antibiotic susceptibility testing (AST) results, tolerability, and clinical course of the patient are known. In the face of unknown information (e.g., AST results, tolerability), clinicians and patients would benefit from understanding

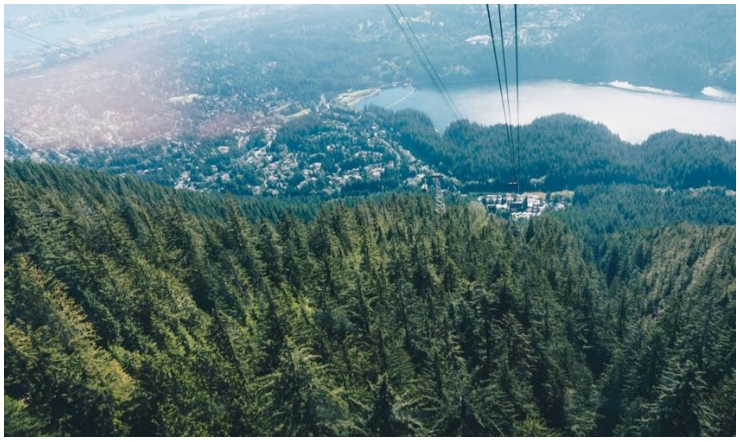
which strategy or sequence of decisions, based on up-to-date information at each step of the way, optimizes the patient outcome and experience.

As another example, consider the management of pregnancy complications. Decisions pre-birth e.g., caesarian have consequences post-birth for the neonate and the mother. Evaluation of strategies that guide pre- and post-birth therapy decisions would be pragmatic, mirroring obstetric treatment decision-making and addressing the most relevant clinical issue: identification of the pregnancy-management strategy that optimizes the ultimate dyad outcomes.

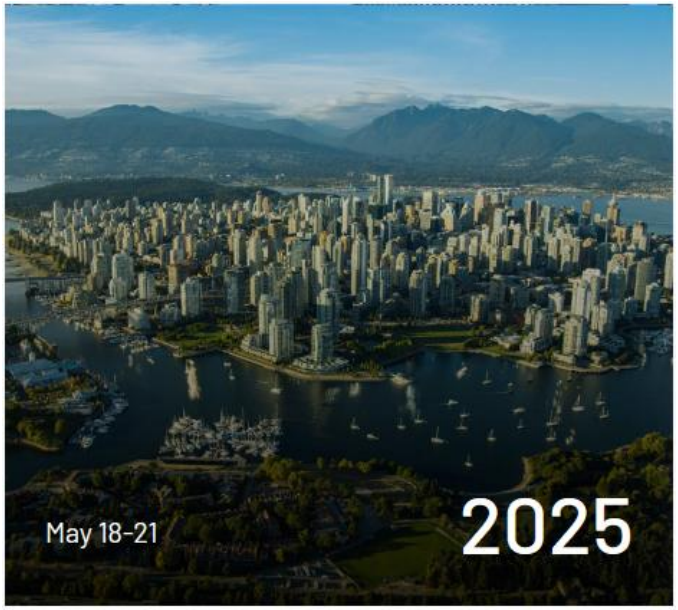
More generally, imagine a marriage of clinical trials and diagnostic medicine with trials that evaluate treatment strategies that involve therapeutic adjustments directed by diagnostic monitoring devices through the course of treatment.

A Glimpse into Vancouver: Grouse Grind and Grouse Mountain

For those seeking rigorous outdoor exercise while in Vancouver, consider the Grouse Grind hike up Grouse Mountain, termed the "Peak of Vancouver." Great views, refreshments, and a wildlife refuge await at the top of the mountain where one can see grizzly bears (named Grinder and Coola) that were orphaned more than 20 years ago. Allow 2.5 hours to complete the hike. The trail is so steep (>2600 feet elevation gained in 1.5 miles) and narrow that downhill hiking is not permitted for safety reasons. A gondola lift is the route down.



"Aerial view of the Grouse Grind and North Vancouver from the tram" (Photo) By Ecoscapes



46th Annual Meeting
Vancouver, Canada