

INVITED SESSION 1 - THE MICRO-RANDOMIZED TRIAL DESIGN FOR DEVELOPING
ADAPTIVE MOBILE HEALTH INTERVENTIONS

ASHLEY WALTON

Micro-randomized trials (MRTs) are a clinical trial design for use in providing data to inform the development of mobile health interventions. MRTs are a type of sequential factorial design in which multiple treatment components are randomized and in which some of the treatment components may be randomized sequentially in time. Thus an individual can be randomized between different options for the treatment component on each of many times resulting in 100's or even 1000's of randomizations per individual during a study. Examples of treatment components in mobile health include whether or not to provide a reminder to take medication and/or different ways to frame the reminders, whether or not to provide suggestions with directions for relaxation exercises and different ways to visualize progress towards health-related goals like daily step count. Treatments are often delivered using notifications on a smartphone or a smart wearable and are delivered in the context of an individual's every-day life. MRTs provide data for use in assessing when and in which context it is most effective to deliver treatments as part of a mobile health intervention. For example, in a MRT used for developing a mobile health physical activity intervention, activity suggestions may be more effective than no suggestion on weekdays but be equally effective as no suggestion on weekends. Or activity suggestions may be more effective than no suggestion at times for which the individual's calendar is not very full. Addressing these types of questions helps investigators decide when it is worthwhile to interrupt the individual to provide the suggestion. The within-person randomization in MRTs is also key to investigating how the effect of a treatment component such as whether to provide an activity suggestion or not varies over time. In general MRTs can provide data that can be used to lead to insights not only about how the effects of time-varying treatments vary over time for a single individual as s/he progresses through the mHealth intervention, but also how these vary between individuals assigned to different treatments at different times.

In this session, speakers who are presently conducting MRTs or have conducted MRTs will describe the rationale behind their studies, discuss challenges and present results. The four MRTs are BariFit, Smart Weight Loss, SARA and JOOLHealth. Each presenter will describe the different scientific questions addressed by their MRT, issues and challenges in addressing those questions, and how the resulting empirical data can inform the development of their just in time adaptive mHealth intervention.

Predrag Klasnja, Assistant Investigator at Kaiser Permanente Washington Health Research Institute, Seattle, will describe a recently completed MRT concerning BariFit, a mobile health lifestyle intervention that leverages activity trackers, digital scales and personalized text messages to provide support to bariatric surgery patients for developing habits (physical activity, food tracking, and regular weigh-ins) associated with successful maintenance of weight loss after

bariatric surgery. This MRT involves multiple treatment components, some of which are randomized at baseline whereas other components are randomized daily, and one treatment component is randomized multiple times per day. The trial was conducted in Seattle, WA.

Inbal Nahum-Shani, Associate Research Professor at the Institute for Social Research, University of Michigan, will present the Smart Weight Loss MRT, designed to optimize the delivery of supportive messaging (via push notifications) to improve self-monitoring behavior among obese/overweight adults participating in a technology-based weight loss program. One component of this MRT is being used to examine the effectiveness of messages to improve self-monitoring that are “value-based” – that include content consistent with the person’s core values. This trial is being conducted in Chicago, IL.

Mashfiqui Rabbi, Postdoctoral Fellow in the Statistics Department at Harvard University, will describe an MRT, currently in the field, concerning the development of Substance Abuse Research Assistant (SARA), which considers engagement strategies to increase self-report completion among 14-24-year-olds at high risk of substance abuse. The engagement strategies are the treatment components in this MRT and include both reinforcement as well as incentive strategies. This MRT will provide data to assist in identifying the optimal delivery timing of reinforcement and incentive strategies in order to improve completion of the self-report data collection measures. In the longer term, SARA will form the basis for a preventive intervention. The SARA MRT is being conducted in Ann Arbor, MI.

Niranjan Bidargaddi, Associate Professor of Health Informatics, Flinders University, Australia, will discuss a recently completed MRT in a commercial setting with a wellness company called JOOLHealth (<https://www.joolhealth.com/>). JOOLHealth is an Android and iPhone based personalized wellbeing intervention that is using an MRT to determine when an app user is most receptive and in need of support offered through push notifications. This MRT randomizes different types of notifications and whether to provide a notification approximately every 3 days. All of the notifications concern a variety of ways to increase engagement in charting daily consistency with the user’s personal goals. The MRT was used to ascertain when the user is most receptive to a notification. The intervention includes a variety of other treatment components including a component that progressively adapts goal-setting tools across time in order to increase behavioral awareness and positive outcomes. This MRT took place across the U.S.

The discussant, Tianchen Qian, Postdoctoral Fellow in the Statistics Department at Harvard University, will contrast these MRTs in terms of their experimental design and will describe power planning resources available for those interested in developing an MRT. Additional examples will be provided for how MRTs can be used to address other public health issues including smoking cessation and medication adherence.

Contributors

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INVITED SESSION 2 - ADAPTIVE TIMING OF INTERIM ANALYSIS FOR PRIMARY EFFICACY OUTCOME

YUKO PALESCH

Interim analysis to ascertain overwhelming efficacy or futility of the primary efficacy outcome in a clinical trial is a common feature, in the form of group sequential design or other pre-specified adaptations. Some study sponsors require at least one interim analysis during a trial.

One key assumption in all forms of interim analysis is that, at the time of interim analysis, personal characteristics and behavior (including response to study intervention) and medical care of future study subjects, will remain similar, if not the same, as those who have completed the protocol (i.e., subjects whose outcome data are analyzed at the interim analysis).

In fact, particularly for large multi-site trials, there are many trial implementation and temporal factors that lead to violations of the aforementioned constancy assumption. There is a learning curve (sometimes very steep) of site personnel in managing the trial and study participants. Many of these trials initiate clinical sites gradually over a period of time due to a variety of logistical and administrative issues (e.g., contracts, personnel availability, drug supplies, etc), which then prolongs the learning curve for the study overall. Furthermore, the composition of sites participating in the trial often changes over time. Finally, another trial may finish, and its results are made public which may affect the ongoing trial, such as equipoise about the treatment, patient recruitment, study drug supply, new regulatory requirements, etc. These mostly subtle effects may contribute to unpredictable trends in the ongoing trial's accumulating primary outcome data over time. This fluctuation could lead to an interim analysis resulting in an overwhelming positive or negative treatment effect (TE) on a random high or low, which, in turn, leads to a potentially incorrect decision to stop the trial. The concept of fluctuation of the TE herein differs from precision of the TE.

We propose an automated method whereby the timing of the first interim analysis is adaptively selected as a function of the stability in the TE estimate over time. The central study database can be programmed to automatically monitor the stability in the TE estimates, and as data accumulate, the system will trigger an alert to the unblinded study statistician when the information is sufficiently stable to conduct the first interim analysis. With this method, the timing of the interim analysis should not compromise blinding. To implement, the definition of stability requires a priori specifications (e.g., the difference in treatment effect from time $t-1$ to time t must be $< X\%$ for Y consecutive t s); and simulation studies may be required to validate the design properties.

Some trials may never reach that stable TE and may require the trial to enroll the maximum sample size. The Albumin in Acute Stroke Part 2 (ALIAS) Trial represents one such case. Had the proposed algorithm been implemented, it may have had to enroll its maximum samples size. Another similar trial that was conducted in the same time period as ALIAS, the Interventional Management of Stroke (IMS) III trial, had the time trend profile of what is normally anticipated –fluctuating early on but becoming stable after a few hundred subjects. In this trial, could we have done the interim analysis sooner than the pre-specified time?

The caveat of the proposed adaptive timing of the interim analysis is that the outcome data in the database need to be current and relatively accurate/clean throughout the trial. However, this is a quality any data management team should strive for regardless of interim analysis. Also, this approach excludes monitoring of safety outcomes, since they are critical data to be reviewed by the study team and the DSMB according to their respective specifications.

Yuko Palesch, a biostatistician and PI of the Statistical and Data Management Center for the ALIAS and IMS trials, will introduce trials as motivating examples and provide an overview of the proposed design. Wenle Zhao will describe how to operationalize and incorporate the proposed design into the study database. Christopher Coffey will discuss how this approach might affect the workflow for the DSMB. Michael Hill will provide clinical perspective on the proposed design. Each speaker will have 20 minutes, followed by an open Q&A period for 10 minutes.

Contributors

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INVITED SESSION 3 - KEEPING YOUR EYE ON THE ENDPOINTS: STUDY CLOSEOUT STARTS FROM THE BEGINNING

DIXIE ECKLUND

Study closeout is a time of reckoning: the data is collected—now is the time to find out what the results have to say! Despite heroic efforts, you may inevitably arrive at this point and realize that the data you collected are not quite in the shape you expected. Missing data, discrepant data, data that requires coding, unresolved deviations, expired regulatory documents, drug accountability incomplete...the list goes on and on. We will discuss how to harness the power of multi-disciplinary clinical research teams to sharpen and maintain the focus on key study endpoints and operational deliverables. Using examples from NeuroNEXT, NETT, StrokeNET, and NEALS, representatives from three coordinating centers will describe how envisioning the study endpoints throughout the life cycle of a trial can improve the quality of your trial, streamline the closeout process, and prevent unpleasant surprises when it is time for data analysis and reporting. Presentations will feature real-world examples of problems that clinical trial teams experienced during study close-out, data analysis, and reporting—and offer lessons learned and tested solutions to these problems. Presenters will speak for 15 minutes followed by an interactive panel discussion for the final 30 minutes.

Dr. Eric Foster will provide insight from a statistician's perspective as to how to organize teams from the beginning to establish data collection techniques for precise study outcomes/endpoints, the importance of including biostatisticians' input during the development of data collection methods and tools, the impact of an interim analysis on early data cleaning, and statistical techniques to clean data as the trial is ongoing.

Catherine Dillon and Trevis Huff will discuss study closeout from a data management perspective and cover effective approaches to data management, performing data cleaning throughout the trial, recognizing patterns of missing data early on, tools for data reconciliation, crafting clear and effective data transfer agreements, and tools for tracking study status with an emphasis on deliverables.

Julie Qidwai will present the perspective of the clinical monitor and will discuss close-out visits and final monitoring reports, risk-based monitoring strategies ongoing during the trial, maintaining consistency in adverse event and concomitant medications coding as well as protocol deviation categorization, PI sign-off of data, and methods for data de-identification and preparation for data sharing.

Marianne Kearney Chase will provide perspectives from a clinical coordinating center on closing out the site regulatory binders and trial master file, completing equipment and drug accountability, closing out multi-site trials with a central IRB, and collaborating with all partners to achieve final data lock, publication, and data sharing.

Applying any one of these approaches will improve your clinical trial—but implementing as many as possible while keeping your eye on the study endpoints can eliminate those end-of-study “surprises”!

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INVITED SESSION 4 - INFORMED CONSENT AND INNOVATIVE TRIAL DESIGNS

SPENCER HEY

Description of Session:

The current ethical requirements for informed consent arose in the middle to late 20th century, when most clinical trials were two-arm randomized controlled trials (RCTs), comparing an experimental drug to a placebo or the standard of care. However, investigators in many areas of biomedicine and health policy are increasingly relying on alternatives to the traditional RCT, and these alternative designs present new challenges for informed consent requirements.

For example, breakthroughs in understanding the biological mechanisms of disease have given rise to new kinds of explanatory trial designs, some of which forgo randomization altogether and instead attempt to match participants to therapies that target particular molecular biomarkers. However, by folding biomarker diagnostics into the therapeutic pathway, these designs may introduce new risks and uncertainties that may need to be disclosed to patients.

At the pragmatic end of the trial design spectrum, there is an increasing awareness of the need for trials that can more directly inform decision-making and policy. This has led to greater use of pragmatic cluster randomized trials (pCRTs). Because such trials are often comparing interventions already in use, implementation of cluster randomization is increasingly being assumed to mean a waiver of consent. Yet, experimenting on human subjects without consent is notoriously controversial, and therefore it is essential to critically examine the conditions for such waivers.

The primary goals of this session are to (1) familiarize the audience with some of the new methodological advances and challenges in trial design; and (2) discuss how these advances, which span the explanatory-pragmatic spectrum, may require comparable advances in the ethical analysis and implementation of informed consent.

The session will be split into two parts: In the first part, we will discuss biomarker-based designs, beginning with the methodological characteristics of the trials, followed by a discussion of the implications for informed consent. In the second part, we will discuss pragmatic cluster randomized trials that test an individual-level intervention, again beginning with an overview of the methodology followed by an ethical analysis. Each part will conclude with audience questions and discussion.

Part 1: Biomarker-Based Designs and Master Protocol Trials

Methodology: Lindsay Renfro [15 minutes]

New biological insights into the pathways of disease has unlocked the possibility for using “predictive biomarkers”—detectable properties of a patient’s specimen that indicate their likelihood of benefiting from a particular therapy. For example, many cancers are no longer defined in terms of their anatomical origin, but rather in terms of the tumor’s molecular biomarkers (e.g., HER2-negative breast cancer, ALK-mutated lung cancer), and therapies can also now be designed to “hit” these biomarker targets, inhibiting the expression of the particular genes or proteins

hypothesized to be driving the disease. Several innovative types of trial designs are now being used to evaluate this new treatment modality. These new designs include interaction designs, which evaluate the efficacy of targeted therapies in patients with and without the biomarker; enrichment designs, which restrict enrollment to patients that have the biomarker of interest; and marker strategy designs, which compare the biomarker-based treatment strategy to a treatment strategy that does not use the biomarker information.

Ethics: Spencer Hey [15 minutes]

The dramatic therapeutic responses with some biomarker-targeting therapies—such as imatinib for Bcr-Abl chronic myelogenous leukemia and vemurafenib BRAF V600 mutated metastatic melanoma—has helped to usher in the era of “personalized” and “precision” medicine. However, the number of biomarkers with targeting therapies remains relatively few, and the evidence base for the majority of biomarkers is still preliminary or theoretical. Thus, the terminology of “personalized” or “precision” medicine may be exacerbating the ethical problem of therapeutic misconception—that is, patients having false or unrealistic beliefs about the likelihood of receiving direct benefit in a trial. Given the discordance between the supporting evidence and the public enthusiasm for personalized medicine, I will argue that particular care needs to be taken in communicating the risks and uncertainties to patients in biomarker-driven trials.

Audience Discussion [15 minutes]

Part 2: Pragmatic Cluster Randomized Trials

Methodology: Monica Taljaard [15 minutes]

Cluster randomization is increasingly being used to advance the pragmatic trials agenda. Cluster randomization can take the form of a simple parallel arm design, but cluster cross-over and stepped wedge designs are becoming popular as they can reduce the required number of clusters. When such designs are embedded within routine clinical practice with waivers of patient informed consent, they have multiple methodological advantages over traditional patient randomized designs. These include a high degree of pragmatism arising from the inclusion of a broad spectrum of patients within routine clinical settings, the avoidance of selection bias when data from all eligible patients are obtained from routinely collected sources, and mitigating risks of treatment contamination and protocol deviations. They also have logistical advantages over patient randomized designs: a trial can be substantially cheaper because only one intervention needs to be implemented in a particular setting at any one time and because there is no patient recruitment, consent, randomization and follow-up for outcome assessment. Finally, pRCTs effectively do away with recruitment challenges faced by many patient randomized trials. Without waivers of consent, these studies may simply not be feasible. The choice of an appropriate trial designs critically depends on the appropriateness of a waiver of informed consent.

Ethics: Charles Weijer [15 minutes]

While cluster randomized designs might be advantageous and logistically convenient, they have multiple ethical challenges which need to be considered prior to their adoption. An important implication of cluster randomization is that, compared to comparable individually randomized designs, they must necessarily expose larger numbers of patients (to a potentially inferior intervention) to reach the same power. Some cluster randomized trials implement individual-level

interventions as a policy at the level of the entire cluster. Research participants may have no way of opting out and avoiding exposure to the trial intervention, and this may undermine trust in the research enterprise. Although there is an ethical guidance document for cluster randomized trials, more work is needed around appropriate justification for the use of this design in the case of individual-level interventions.

Audience Discussion [15 minutes]

Contributors

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INVITED SESSION 5 - OPEN SHARING OF CLINICAL TRIAL DATA

MARC BUYSE

The last five years mark the beginning of a revolution in clinical research: data collected on patients treated in clinical trials to support approval of new drugs and devices, which for a long time were considered confidential, will from now on be shared with a view to enhancing public health and informing future research. In 2013, the European Medicines Agency set a new standard for clinical trial data transparency by enabling interested parties to request data from clinical trials submitted for marketing authorization of medicinal products, including patient-level data (EMA 2013). Other proposals to enable access to clinical trial data were made by the Pharmaceutical Research and Manufacturers of America and European Federation of Pharmaceutical Industries and Associations (PhRMA and EFPIA 2011) and the Institute of Medicine (2015), among many others.

This session will explore the possibility of open sharing of clinical trial data, i.e. without the current constraints including submission of a detailed research proposal, acceptance by a review panel and/or by ethics committees, access to limited data on a dedicated platform, and all such like.

Frank Rockhold will provide a critical review of platforms offering access to clinical data from pharmaceutical industry and NIH-sponsored trials, and will discuss how investigator involvement may extend the concept to academic (investigator-sponsored) trials.

Ena Bromley will draw parallels between clinical data and biological data (such as genotypic or genomic data) that have from the beginning been considered openly shareable.

Marc Buyse will address potential benefits of open data sharing vs. real or perceived concerns related to data confidentiality, with reference in particular to the European General Data Protection Regulation which will become effective in May 2018.

Brian Bot will discuss future perspectives, including open access to all patient data, access to analysis code for reproducible research, and other open access paradigms that could be transformative for future clinical research.

Ample time will be left for a Q&A session after the formal presentations.

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INVITED SESSION 6 - DESIGNING TRIALS WITHIN IMPLEMENTATION LABORATORIES

REBECCA WALWYN

Implementation science can be defined as the “study of theories, process, models and methods of implementing evidence-based practice in healthcare”. Implementation interventions (e.g. audit and feedback) are complex. When two-arm trials have shown that, in general, an intervention package is effective, the next logical step is to establish whether a particular version of that intervention is effective and if this generalizes across settings. The large number of different potential versions of a complex intervention, means that it is likely that a series of trials will be needed to identify the optimal intervention. Implementation laboratories have recently been proposed as a way of utilising existing large-scale service implementation programmes (e.g. national clinical audits) to embed sequential randomised trials that would test different ways of delivering implementation interventions in comparisons at scale. Implementation laboratories involve healthcare system partners in continuous improvement using rigorous methods to identify more effective variants of an intervention that can be routinely and sustainably embedded into their ongoing programs. However, the opportunity of conducting a series of linked large-scale pragmatic trials on similar samples of healthcare providers also raises challenges.

It is therefore important that a range of design choices are considered for randomised trials conducted within these laboratories. Some of these have been used in this context, while others are more typically used elsewhere and need adapting for this purpose. The aim of this session is to provide an overview of a number of possible trial designs, bringing together methodologists from diverse backgrounds to discuss the priorities going forward.

- Talk 1: Introduction to Implementation Laboratories (Jeremy Grimshaw, jgrimshaw@ohri.ca)

This talk will provide an overview of an example of an implementation laboratory for audit and feedback interventions, providing a description of the motivation for establishing implementation laboratories and their potential for moving a field forward. The design challenges associated with conducting a series of trials will be introduced.

- Talk 2: Standard Cluster-Randomised and Stepped Wedge Designs (Monica Taljaard, mtaljaard@ohri.ca)

This talk will summarise the trial designs that are currently used in this context, providing examples, highlighting their limitations and raising points for discussion.

- Talk 3: Sequential Multiple Assignment Randomised Trials (Shawna N. Smith, shawnana@umich.edu)

This talk will provide an overview of trial designs used to optimise an intervention that dynamically evolves over time. While these are typically used to optimise patient-level interventions, consideration will be given to how they may be extended to optimise healthcare provider level interventions common in implementation science.

- Talk 4: Adaptive Designs: Multi-Arm Multi-Stage (MaMS) Trials (James Wason, james.wason@mrc-bsu.cam.ac.uk)

This talk will provide an overview of a specific type of adaptive design that, over time, includes decisions to drop existing, or include new, interventions from an ongoing trial. While these are typically used to evaluate pharmacological interventions, consideration will be given to how they may be extended to evaluate complex interventions.

- Discussant: Discussion: Future priorities (Amanda Farrin, A.J.Farrin@leeds.ac.uk)

This will first summarise the key themes from the previous talks and outline the future priorities based on these. The discussant will then lead a discussion, including speakers and those attending the session, on these priorities.

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INVITED SESSION 7 - COVARIATE CONSTRAINED RANDOMISATION FOR THE DESIGN OF PARALLEL AND STEPPED WEDGE CLUSTER TRIALS

ELIZABETH TURNER

Background

It is common for parallel-arm cluster randomised trials (CRTs) and stepped-wedge (SW) CRTs to enroll a small number of clusters (e.g. < 20 clusters). In this case, the chance of imbalance of baseline covariates for intervention and control conditions is non-negligible. This threatens the internal validity of the trial and reduces power and precision when such covariates are predictive of the outcome. To address the problem of baseline imbalance of covariates in the design phase of parallel-arm and SW-CRTs, a restricted randomisation procedure could be used. Examples include matching and stratification, which are commonly used for the design of parallel-arm CRTs (Ivers 2005). Yet, these techniques have several limitations (e.g. difficulty handling continuous covariates and accommodating multiple covariates) and there is little literature on their application to SW-CRTs.

An alternative restricted randomisation approach that has been proposed for two-arm parallel CRTs is covariate constrained randomisation (CCR; Raab 2001, Moulton 2004). Despite its existence for more than a decade, CCR has been rarely used in practice, possibly because of lack of an easy way to implement the procedure. Yet it offers many benefits thanks to its flexibility to accommodate multiple covariates, both categorical and continuous. These benefits extend to the SW-CRT design but present a range of additional complexities compared to implementation for the two-arm parallel CRT. These complexities arise from the fact that in SW-CRTs the contribution of each cluster-period to the treatment effect estimate differs depending on the location of the cluster-period in the design (Matthews 2017; Girling 2016). Cluster-periods which are closer to the time at which the cluster transitions from the control to intervention condition, for example, carry greater weight than other cluster-periods. Covariate balance criteria used to perform CCR must therefore consider not simply the average of important predictor covariates (such as cluster size) across control and intervention conditions but rather the weighted average of important predictor covariates where the weights are proportional to the weight that the cluster-period provides to the treatment effect.

Overview of proposed session

Our goal is to enable attendees to gain an understanding of key features of covariate constrained randomisation and to leave with a knowledge of tools available to implement CCR for both the two-arm parallel CRT and the SW-CRT designs. To do this, we propose to include four talks followed by a panel discussion with the 4 presenters. In brief, the talks will be as follows, with more details presented below:

1. An introduction to covariate constrained randomisation for parallel two-arm CRTs.
2. Challenges of covariate constrained randomisation for SW-CRTs.
3. Balance metrics for covariate constrained randomisation for SW-CRTs.

4. Practical implementation of covariate constrained randomisation for SW-CRTs.

Talk descriptions

Talk 1 by Liz Turner will provide an overview of covariate constrained randomisation for two-arm parallel CRTs. She will provide an introduction to the principles, including the key concepts of balance criteria and the size of the randomisation space (Li 2015; Li 2017). By using a real-data example of a trial with 16 clusters and 8 cluster-level baseline covariates (Dickinson 2015), she will show how CCR can be implemented using the `cvcrand` command in both Stata and R (Gallis 2018; Yu 2018).

Building from the introduction, in talk 2, Andrew Copas will highlight the specific challenges and complexities of using covariate constrained randomisation for SW-CRTs. To do so, he will present the distinction between balancing across allocation sequences compared to balancing the total intervention vs. control cluster-periods. He will first focus on the example of balancing for a single cluster-level binary covariate and then building to a more realistic example of a SW-CRT with multiple covariates based on the example of a SW-CRT of a package of interventions to reduce pre-treatment loss to follow-up in 14 primary health care facilities in a geographic tuberculosis hotspot in South Africa.

Building from the introduction to CCR for SW-CRTs, in talk 3, Fan Li will formally propose and evaluate a range of balance criteria and for the size of the constrained randomisation space for CCR for SW-CRTs. He will provide simulation-based evidence for why the balance metrics used should weight cluster-periods according to their contributions to the estimation of the intervention effect.

To facilitate the use of CCR for the design of SW-CRTs, in talk 4, Karla Hemming will provide an overview of its implementation using software developed by our team. She will describe implementation using an R-shiny app which allows users to input the design of the study, details of clusters and cluster-level covariates to be included in the constrained allocation; offers various balance metrics, seed specification and then produces a single allocation which balances the design on the covariates and according to the metric specified.

Summary

With the widespread use of CRTs (both parallel-arm and stepped-wedge) with small numbers of clusters to address questions on effectiveness of complex interventions, it is important to be able to design those trials to avoid baseline imbalance on baseline covariates. Through our proposed session in which all authors have jointly contributed to the research presented, we hope to provide an intuitive and comprehensive overview of the method and to provide attendees with practical tools to be able to go away with the knowledge of how to implement the proposed methods. We propose to use the final 20 minutes of the session for a moderated panel discussion with time for questions from the audience.

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INVITED SESSION 8 - CLINICAL STUDIES WITH LONG-TERM FOLLOW-UP: EXPERIENCES AND LESSONS LEARNED

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Introduction: Most clinical trials enroll subjects and follow them for a limited time (typically 1-5 years) and are designed to address specific questions, such as the effect of an intervention with respect to a primary outcome (e.g. cardiovascular disease incidence). Although of interest, investigating other secondary outcomes (e.g. mortality, cancer) is challenging due to the limited follow-up. A long-term follow-up study of a cohort after completion of a study allows for the investigation of such outcomes and provides a more thorough description of the effect of an intervention on the entire burden of disease.

Many scientific and management challenges are associated with conducting long-term follow-up studies. This session will present how three different impactful studies with varying study designs and populations and long-term follow-up have dealt with changes over time. Specifically, changes in primary and secondary aims, study design, outcomes and exposures of interest, data management and collection, electronic records and registries, study organization, and funding mechanisms over time. The statistical methods to account for these long-term changes will be described. Each presenter will also discuss issues related to patient retention and investigator/staff turnover in studies that span decades. The challenges and approaches experienced in these three studies are relevant to many longitudinal studies.

Outline of Talks (three 20 minute talks):

- Background (disease, historical considerations, etc)
- Changes over time in primary and secondary aims, study design, outcomes and exposures of interest, data management and collection (modernization of systems and labs), electronic records and registries, study organization, and funding mechanisms.
- Statistical methods to account for these changes over time
- Patient retention, investigator and staff turnover
- Lessons learned / Next steps

Talk 1 (20 min): Dr. Barbara H. Braffett will present the Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The DCCT (1982-1993) was a clinical study in type 1 diabetes funded by the National Institute of Diabetes and Digestive and Kidney Diseases was designed to test the glucose hypothesis in 1,441 subjects with type 1 diabetes. After an average of 6.5 years of follow-up, the DCCT successfully demonstrated the beneficial effects of intensive diabetes management in reducing the early stages of microvascular disease by 35-76%. The observational follow-up study, EDIC (1994-present), is currently in its 33rd year of follow-up and has shown the durable effect of intensive therapy as well as additional risk reductions in severe complications, CVD, and mortality.

Talk 2 (20 min): Dr. Ian Ford will present the West of Scotland Coronary Prevention Study (WOSCOPS). The WOSCOPS, a primary-prevention study of 6,595 men aged 45-64 years with elevated cholesterol levels, demonstrated that an average of 4.9 years of statin-therapy significantly reduced the risk of nonfatal myocardial infarction or death from cardiovascular disease by 31%. The extended follow-up study continues to monitor the use of statin-therapy and assess the ongoing safety and efficacy using electronic record linkage to national databases of hospital discharge summaries, incident cancers and deaths. The extended follow-up has demonstrated long-term cost effectiveness, safety and continuing benefit in preventing deaths and incident cardiovascular hospitalizations. Currently, follow-up results up to 20 years post randomization have been published,

Talk 3 (20 min): Dr. Janet Tate will present the Veterans Aging Cohort Study (VACS). VACS (1997-present) is an open cohort of all HIV positive US Veterans receiving care from the Veterans Health Administration (VA), each matched to two uninfected comparators by age, sex, race and site of care. Established in 2004 with 100,000 patients (33,400 HIV+) the cohort was fully updated in 2008, 2010, 2012 and 2015. A total of 164,000 patients (53,000 HIV+) are now in the study. Of those not known dead, 83% had a VA visit in the last year. The primary data source is the VA electronic health record (inpatient and outpatient encounters including diagnoses, vital signs and procedures; laboratory results; pharmacy fills) supplemented by linkage to Medicare and National Death Index records. To extend beyond medical records, a sub-cohort of consented patients at 8 sites began enrollment in 2002. All complete a baseline survey with follow-ups offered every 12-18 months. Now in its 9th wave, 8,750 participants have completed 35,400 surveys including domains ranging from alcohol and drug use, depression, physical function and symptoms. Among other accomplishments, the group developed and externally validated the VACS Index, a prognostic model for all-cause mortality, cause specific mortality, and other outcomes in those living with HIV infection.

Discussant (10-15 min): Dr. Ionut Bebu will summarize the themes presented in all three studies and compare and contrast the strategies and mechanisms employed to successfully continue these longitudinal studies. The discussion will emphasize the common approaches and solutions which can be relevant to other similar clinical studies.

Round Table (15-20 min): Dr. John M. Lachin will lead the panel discussion and Q/A session.

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Ionut Bebu
John Lachin

INVITED SESSION 9 - CURRENT DEVELOPMENT OF ADAPTIVE DESIGNS IN CLINICAL TRIALS

LI CHEN

Current development of adaptive designs in clinical trials will be discussed. The session have two focuses: (1) to present the motivation, design and results of the DIA Adaptive Design Scientific Working Group (ADSWG) survey for the perception and use of adaptive designs in industry and academia from 2012 to 2015; (2) to demonstrate innovative adaptive designs utilized in both early and late phase clinical trials given the new challenges in drug development.

To understand trends regarding the extent and types of usage of adaptive designs across industry and academia, the ADSWG formed a drug and biologics survey subteam whose role was to gather this information; the first survey was conducted in 2008 and was primarily case-study based. A second, expanded survey was conducted in 2012. The comprehensive findings of a third survey conducted in 2016 are presented here. Both the 2012 survey and the 2016 survey consist of data collection, a literature review, and a trial registry review. Comparisons of the latest two DIA ADSWG Surveys, those conducted in 2012 and in 2016, are provided with recent adaptive design (AD) surveys carried out by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Changes to the methodology to capture how the field has been changing and to maintain information to be able to study trends over time will also be discussed.

The second part of the session will focus on how innovative adaptive designs in both early and late phase clinical trials have been implemented to overcome the challenges we are facing in drug development. For example, the clinical efficacy Proof-of-Concept (PoC) stage is an important milestone before an investigational drug progresses into late stage development. A PoC study is often the first time the drug is tested in the potential target patient population. There is strong incentive to conduct adaptive trials in the PoC stage to help utilize data and conduct trials more efficiently. On the other hand, PoC studies are usually conducted with a short term intermediate endpoint such as biomarkers for time and resource consideration, and therefore there are uncertainties around the predictive value of a biomarker selected and validated in the PoC studies especially its predictive value in the primary efficacy outcomes. Examples of PoC adaptive designs and biomarker adaptive designs using intermediate endpoint for population selection and enrichment in Phase 3 settings will be presented.

The title and brief abstract of each speaker's talk is listed below:

(1) Li Chen, Amgen Inc.

DIA Adaptive Design Scientific Working Group 2016 Survey on Perception and Use of Adaptive Designs: Methodology and Results

The objective of the ADSWG's effort was to provide insight on the perception and use of adaptive designs for clinical development programs in both the pharmaceutical industry and academia for drugs and biologics. Have adaptive designs become more commonplace? Have specific adaptations become more accepted or useful? Are there still barriers to designing or implementing clinical studies with adaptations? This presentation will provide the motivation, design methodology from

the 2016 survey and results on the usage and any persistent barriers to implementing adaptive designs.

(2) Eva Miller, Independent Biostatistical Consultant

DIA Adaptive Design Scientific Working Group Survey Results over time Compared to Recent Survey Results Published by CBER and CDRH and the EMA

In this presentation, DIA ADSWG's most recent results in 2016 will be compared with previous two survey results and displayed over 3 four-year time periods of 2004-2007, 2008-2011, and 2012-2015. Results are also compared with the survey results published by CBER and CDRH and the EMA. Trends from the various surveys are identified, recommendations for overcoming implementation challenges are given.

(3) Frank Fan, Novartis

Adaptive Design Applications in Proof-of-Concept Clinical Trials

There is lower health authority concerns with using AD in the early development stage than in the late phase. However there are unique issues from less known drug information, uncertain treatment effect and dose response, and more cost constraint for designs in this setting. In this talk, some innovative adaptive designs which have been used in the Proof-of-Concept clinical trials will be discussed.

(4) Nicole Li, Merck Co.

Adaptive Phase III Designs with Biomarker Population Enrichment

In the era of personalized medicine, based on the mechanism of action, an investigational new drug may have greater treatment effect in a biomarker positive population than in the biomarker negative population. However, limited by preclinical data and early phase clinical data, many Phase 3 confirmatory trials are initiated without fully understanding the biomarker effect. In this presentation, an adaptive design on biomarker population enrichment with opportunity to discontinue the biomarker negative population is proposed. We also propose using an intermediate endpoint for the interim population adaptation and will discuss the advantages and disadvantages of using intermediate endpoints for interim population adaptation. Since data are used to modify the study population and hypothesis testing, depending on the timing of the interim analysis and the correlation between the intermediate endpoint and the primary endpoint, nominal type I error at the final analysis will be adjusted to ensure the overall type I error is tightly controlled. An illustrating example will be given to demonstrate the operating characteristics of the proposed design. In addition, when there is no desire to discontinue any population mid-trial, two alternative adaptive designs that pay no penalty on Type I error will also be proposed.

(5) Roger Lewis: Berry Consultants

Discussant

Contributors

Li Chen

Li Chen

Eva Miller

Frank Fan

Nicole (Xiaoyun) Liu

Roger Lewis

INVITED SESSION 10 - THE ROLE OF CENTRAL IRB VS DSMB IN THE DECISION MAKING
PROCESS FOR PREMATURE TERMINATION OR ENROLLMENT SUSPENSION OF A
MULTICENTER TRIAL

SHARON YEATTS

Use of a central or single Institutional Review Board (cIRB/sIRB) is thought to improve the quality and efficiency of ethical oversight in multi-center clinical trials. The revised Federal Policy for the Protection of Human Subjects in Research, which is set to go into effect in January of 2018, mandates single IRB review for federally funded research. The US Food and Drug Administration (FDA) is required to harmonize with these regulations as a result of the 21st Century Cures Act and has indicated that it does intend to follow that mandate. These revisions follow many initiatives along the same lines.

The Clinical Trials Transformation Initiative (CTTI) issued Recommendations on Advancing the Use of Central IRBs for Multi-center Clinical Trials in 2015 to facilitate the adoption of cIRBs/sIRBs for multi-center clinical trials. And, in June 2016, NIH released a policy notice (NOT-OD-16-094) that requires the use of a cIRB/sIRB, as the IRB of record for multisite non-exempt human subjects clinical research funded by NIH and conducted in the US. Clinical trial networks funded by NIH (e.g., StrokeNet, NeuroNEXT, SIREN) have designated their respective cIRB/sIRB.

For many clinical trials, the NIH policy requires that data quality and safety also be reviewed by a Data and Safety Monitoring Board (DSMB). The DSMB is charged with approval of the protocol prior to study initiation, regular (often semi-annual) review of the accumulating safety data, and formulation of recommendations to the sponsor regarding whether enrollment should continue or terminate prematurely. The distinction between the cIRB/sIRB and the DSMB, in terms of certain of their roles and responsibilities, can become blurred.

Consider a multisite trial where each site's IRB serves as its IRB of record. If the IRB found irregularities (for example, higher than anticipated incidences of an adverse event) in the trial, either at its site or at another site participating in the trial, it could suspend enrollment or stop trial activities ONLY at its site. In contrast, when a cIRB/sIRB is the IRB of record, decisions to suspend enrollment for a non-site-specific reason would generally apply to ALL participating sites. Meanwhile, the DSMB also could make a recommendation to the sponsor that enrollment be suspended or the trial be terminated, a recommendation which would affect all sites. . This apparent overlap in scope of oversight has the potential to cause confusion and controversy. What happens if the cIRB and the DSMB disagree in their decision? What is the order, if any, of the decision making process? What information and data need to be shared with cIRB/sIRB and the DSMB?

The session will begin with presentation of a recently terminated trial* by the study statistician (Yeatts), followed by commentary from its cIRB (Linke) and DSMB (Parides) members describing the experience from their respective viewpoints. Then, a panel of experts from another cIRB (Russell-Einhorn), DSMB (Ellenberg), and clinical team (Silbergleit) will present and discuss their perspectives on this topic.

*Study results presentation/disclosure is pending at the time of abstract submission; however, the specific case study should be open for discussion by the time of the SCT in May 2018.

Suggested Speakers:

Example case study background - Sharon Yeatts (10 min)

Case cIRB perspective – Michael Linke (15-20 min)

Case DSMB perspective – Michael Parides (15-20 min)

Panel Discussion (40-45 min):

General cIRB view – Michele Russell-Einhorn, Schulman IRB

General DSMB view – Susan Ellenberg

General Clinical PI perspective – Rob Silbergleit

Contributors

Yuko Palesch

Sharon Yeatts

Michael Linke

Michael Parides

Michele Russell-Einhorn

Susan Ellenberg

Robert

INVITED SESSION 11 - RECENT DEVELOPMENTS IN UMBRELLA, BASKET AND PLATFORM TRIAL DESIGNS

YING YUAN

The conventional trial paradigm — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. The conduct of “precision medicine” trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. Umbrella, basket, and platform trials are three major trial design innovations responsive to these challenges.

In this session, we invited three experts in the fields to discuss some recent developments in this frontier. Specially, Dr. Jun Yin will present a novel a statistical framework for designing and conducting umbrella trials, where the individual biomarker-specific cohorts are randomized studies comparing the targeted agents vs. consolidated control arms. Dr. Ying Yuan will present a novel basket trial design that accounts for cancer type heterogeneity and allows adaptive information borrow across different cancer types. Dr. Jack Lee will present Adaptive multi-arm platform designs for efficient drug development.

Our session is suitable for biostatisticians and clinicians in academia, government and industry.

Speakers: Jun Yin, Mayo Clinic

Jack Lee, MD Anderson Cancer Center

Ying Yuan, MD Anderson Cancer Center

Abstracts:

An Adaptive Biomarker-driven Phase II Design

Jun Yin, Qian Shi

The paradigm for cancer clinical trials has shifted towards individualized treatment due to the blooming discoveries of biomarkers and targeted agents. Because of the deficiencies of screening agents one at a time, a new type of umbrella trials is emerging where patients with a common disease type are enrolled to parallel cohorts that are biomarker driven. We introduce a statistical framework for designing and conducting such umbrella trials, where the individual biomarker-specific cohorts are randomized studies comparing the targeted agents vs. consolidated control arms. The proposed design allows the parallel cohorts to be dynamic, so that at interim analysis investigators can 1) eliminate or graduate marker/treatment cohorts, and 2) cluster marker/treatment cohorts to improve the efficiency and power to identify promising targeted agents. The design is calibrated with respect to specific error rates. We conduct extensive simulations to assess the performance of the proposed design with comparison to sequentially conducted randomized two-arm trials, and illustrate it with an Alliance NCTN coordinated trial in progressive meningiomas with SMO/AKT/NF2 mutations (A071401).

BLAST: Bayesian Latent Subgroup Design for Basket Trials Accounting for Patient Heterogeneity

Ying Yuan, Ph.D.

The basket trial refers to a new type of phase II cancer trial that evaluates the therapeutic effect of a targeted agent simultaneously in patients with different types of cancer that involve the same genetic or molecular aberration. Although patients enrolled in the basket trial have the same molecular aberration, it is common for the targeted agent to be effective for patients with some types of cancer, but not others. We propose a Bayesian latent subgroup trial (BLAST) design to accommodate such treatment heterogeneity across cancer types. We assume that a cancer type may belong to the sensitive subgroup, which is responsive to the treatment, or the insensitive subgroup, which is not responsive to the treatment. Conditional on the latent subgroup membership of the cancer type, we jointly model the binary treatment response and the longitudinal biomarker measurement that represents the biological activity of the targeted agent. The BLAST design makes the interim go/no-go treatment decision in a group sequential fashion for each cancer type based on accumulating data. The simulation study shows that the BLAST design outperforms existing trial designs. It yields high power to detect the treatment effect for sensitive cancer types that are responsive to the treatment, and maintains a reasonable type I error rate for insensitive cancer types that are not responsive to the treatment.

Adaptive multi-arm platform designs for efficient drug development

J. Jack Lee, Ph.D.

The current clinical trials system of screening new agents is typically one agent and one trial at a time, which is inefficient, expensive, and time consuming. To address these deficiencies, we introduce a statistical framework for designing and conducting randomized multi-arm screening platforms with binary endpoints using the Bayesian modeling. In essence, the proposed adaptive platform design consolidates inter-study control arms, enables investigators to assign more new patients to novel therapies, and accommodates mid-trial modifications to the study arms that allow both dropping poorly performing agents as well as incorporating new candidate agents. When compared to sequentially conducted randomized two-arm trials, screening platform designs have the potential to yield considerable reductions in cost, alleviate the bottleneck between phase I and II, eliminate bias stemming from inter-trial heterogeneity, and control for multiplicity over a sequence of a priori planned studies. When screening five experimental agents, our results suggest that platform designs have the potential to reduce the mean total sample size by as much as 40% and boost the mean overall response rate by as much as 15%. Both the posterior probability and predictive probability approaches can be applied to the platform designs. The gains in efficiency by platform designs could speed up the time of drug development and increase the success rate of identifying efficacious agents.

Contributors

Yong Zang
Jun Yin
Jack Lee
Ying Yuan

INVITED SESSION 12 - WHAT ARE WE LEARNING FROM PRAGMATIC CLINICAL TRIALS?
DESIGN, IMPLEMENTATION AND ANALYTIC STRATEGIES

CATHERINE MEYERS

What Are We Learning from Pragmatic Clinical Trials? Design, Implementation and Analytic Strategies

Several different US research organizations have been conducting pragmatic clinical trials (PCT) in a variety of health care settings. Pragmatic clinical trials provide an opportunity for testing interventions in real-world settings, as they embed trial interventions into routine clinical care delivered by health care systems. As a number of large-scale pragmatic clinical trials have been launched and completed within these organizations, much has been learned regarding their unique design, implementation and analytic challenges. This session will describe recent efforts from these programs that have focused on performing PCT across many health care delivery organizations, including those within academic, corporate and federal systems. Studies conducted thus far have provided important lessons learned for both planning and implementation of future pragmatic trials. The panel includes scientists from the Patient-Centered Outcomes Research Institute, the US Department of Veterans Affairs Point of Care Research program, and the Health Care Systems Research Collaboratory supported by the National Institutes of Health; and will use ongoing PCT as case studies for specific challenges that must be addressed for successful trial implementation.

Moderator – Catherine Meyers

Perspectives from the Patient-Centered Outcomes Research Institute (PCORI) – Jason Gerson

This presentation will briefly characterize PCORI's portfolio of PCT, which are intended to generate robust and real-world evidence about the comparative effectiveness of known efficacious interventions. These trials are designed and conducted under conditions meant to reflect the decisional context faced by patients and providers, and strive to mimic the actual use conditions under which the intervention(s) would be applied. The presentation will then describe several critical issues concerning the design and implementation of PCT, including the extent to which non-adherence (both provider and patient) should be monitored and remedied, and the inclusion of patient-reported outcome data not routinely collected as part of clinical practice. Strategies for how these issues were addressed in ongoing trials will further illustrate how investigators can enhance planning efforts for future work.

Veterans Affairs Point of Care Research (POC-R) Program – Ryan Ferguson

This presentation will highlight the progress to date and lessons learned from a large PCT embedded within the VA Healthcare System's electronic medical record. This clinical trial, the Diuretic Comparison Project, is aimed at testing the comparative effectiveness of two common antihypertensive medications at preventing cardiovascular outcomes in Veterans over age 65 with hypertension. Topics addressed will focus on real-world strategies for leveraging the use of the electronic medical record for patient phenotyping, outcome ascertainment, safety surveillance, and communication with healthcare providers.

Health Care Systems Research Collaboratory, National Institutes of Health – Robin Boineau

The NIH Collaboratory has launched several PCTs embedded within a variety of health care systems across the US. This presentation will focus on several aspects of health care systems interactions for clinical investigators and their teams, which must be addressed in both the planning and implementation phases of a PCT. In view of the ever-changing landscape of health care delivery, all Collaboratory teams worked closely with their health care system partners to address challenges in planning for trial initiation (intervention delivery and EHR) and after trial initiation (staff changes, maintaining intervention delivery, reliable data collection via the EHR). Specific case study examples from the NIH Collaboratory will be presented, with lessons learned on strategies of future investigators as they partner with health care system leadership.

Lessons from Pragmatic Clinical Trials for Pain Management – Lynn DeBar

This presentation will highlight study design and methodological issues involved in embedding a complex behavioral intervention into the primary care setting (multidisciplinary treatment for patients with chronic pain on opioid treatment). Issues to be discussed include implications of cluster randomized approaches, intervention staffing, collection of patient reported outcomes, and the culture and infrastructure of primary care settings for integrating the PCT into the clinical work flow and potential sustainability. Effectiveness-implementation hybrid designs will also be described, as a potentially beneficial framework for these types of PCT.

Pragmatic Clinical Trial Methodologic & Analytic Strategies –Patrick Heagerty

Embedded PCT within health care systems provide opportunities for efficiently answering important research questions that can improve clinical care. Several PCT conducted with US programs thus far have presented design and analytic challenges that were addressed in the trial planning phase. As these programs have launched several PCT across many disciplines, centralized Design & Biostatistics Working Groups were created within the programs to facilitate trial planning, and to develop methods and best practices for future research. This presentation will describe specific methodologic challenges for the planning of cluster-randomized PCT, including design, randomization strategy, assumptions for sample size and statistical analysis. Case studies from both PCORI and the NIH Collaboratory programs will describe approaches that have been successful, and highlight a process that maximizes scientific rigor across PCT programs.

Contributors

Catherine Meyers
Jason Gerson
Ryan Ferguson
Robin Boineau
Lynn DeBar
Patrick Heagerty

INVITED SESSION 13 - INTRODUCING THE NEW CONSORT EXTENSION FOR THE STEPPED-WEDGE CLUSTER RANDOMISED TRIAL

KARLA HEMMING

Background: The stepped-wedge cluster randomised trial (SW-CRT) is a novel cluster randomised trial variant that is particularly valuable to evaluate health service delivery interventions that is increasingly being used. It is particularly relevant for evaluating service innovations in learning healthcare organisations. The SW-CRT involves randomisation of clusters to different sequences that dictate the order at which each cluster will switch to the intervention condition.

Whilst only about 40 completed SW-CRTs are currently listed within Pubmed, there has been an exponential increase in the use of this design over the past few years with an expected increase in publications in the near future. There are multiple other indicators of the upward trajectory of the design, included NIHR funded methodological grants; dedicated conferences to the design; highly cited methodological papers and over 100 stepped wedge trials listed on the three main trial registries as “ongoing”.

A number of systematic reviews have demonstrated poor reporting of key methodological features of SW-CRTs leading to our project to develop a SW-CRT CONSORT extension. We used EQUATOR endorsed methodology and have had full engagement with the EQUATOR group throughout the process. This statement has been produced with involvement with many of the leading experts in this particular study design, and journal editors, ethicists, statisticians, methodologists, and developers of reporting guidelines. The reporting guideline highlights the additional complexities of the design.

In this panel session we will report on this extensive piece of work, this will include the background preparatory work identifying current quality of reporting against various metrics; summarise the key methodological unique features of this trial design which require special consideration at the reporting stage; describe key Items added to the CONSORT extension; and illustrate a novel crowd-sourcing methodology to perform an early validation study of the guideline.

Introduction: This talk will consist of a brief introduction to the SW-CRT and include a description of a case study which will be used through-out the session. A wide variety of terminology has been used to describe aspects of the SW-CRT design. For the purpose of this session, the key components of the design will be outlined and a glossary of terms provided.

Talk one: Results from systematic reviews examining the quality of reporting of SW-CRTs.

We conducted several systematic reviews in advance of the consensus process. This talk will summarise these reviews. We identified that the SW-CRT is increasingly being used and that the majority of trials are conducted in advanced economies and in healthcare settings; although a significant minority are conducted in lower middle income settings.

Reviews of the quality of reporting of sample size and analysis methods revealed incomplete or inadequate reporting overall, and specifically, lack of reporting of how time effects and extended correlation structures were incorporated both at the design and analysis stages. Reviews of the

ethical conduct and reporting revealed that many SW-CRTs do not report research ethics review; do not clearly identify from whom and for what consent was obtained; and a significant number do not pre-register with a trial registration database.

Talk two: An exploration of the key properties of the SW-CRT which require special consideration in their reporting.

This talk will explore the key aspects of the SW-CRT which are associated with bias. Clear reporting of these aspects is essential to facilitate interpretation of trial results in published reports. Firstly, time is a potential confounder in a SW-CRT and requires special consideration both at the design and analysis stage. Secondly, as the SW-CRT is a longitudinal and clustered study, correlation structures are more complex than those of a parallel CRT carried out at a single cross-section in time. Thirdly, some SW-CRTs are at risk of within-cluster contamination. Within-cluster contamination can arise either when outcomes in the intervention condition are obtained from participants who are yet to be exposed to the intervention, or alternatively, when outcome assessments in the control condition are from participants already exposed to the intervention. Contamination arising from observations yet to be fully exposed to the intervention condition can be allowed for by building in transition periods into the design; or by modelling these effects (referred to as lag effects) [Hughes 2015]. Interactions between time and treatment can also arise. These time varying effects are more likely to arise when the intervention is not continuously delivered, does not create a permanent change, or where its impact might wain or grow over time.

Talk three: The CONSORT extension for Stepped-Wedge Cluster Randomised Trials: summary of key Items to report.

This talk presents the Consolidated Standards Of Reporting Trials (CONSORT) extension for the stepped-wedge cluster randomised trial (SW-CRT). The development of this statement was motivated by the unique design characteristics of the stepped wedge design, including the need to allow for time effects and because the design is increasingly being used. The guideline was developed using a Delphi survey and consensus meeting; and is informed by the CONSORT statements for individually and cluster randomised trials. Reporting items along with explanations and examples are provided.

An early assessment of the validity of the statement and quality of reporting according to the new guideline – using a novel crowd-sourcing methodology. This talk presents the results of a systematic methodology review to assess the quality of reporting of recent SW-CRTs according to the new guideline. This will provide a baseline assessment for which improvement in quality of reporting will be assessed, by repeating the process in several years' time. Importantly the review also reports an assessment of validity of the statement, as each quality assessment was performed independently, randomly and in duplicate by more than 50 assessors.

Contributors

Jeremy Grimshaw
Karla Hemming
Monica Taljaard
Michael Grayling

INVITED SESSION 14 - COMPETING WITH RVUS: HOW TO SUCCESSFULLY BALANCE
CLINICAL RESEARCH AND CLINICAL PRACTICE FOR THE ACADEMIC CLINICAL PRINCIPAL
INVESTIGATOR

VALERIE DURKALSKI-MAULDIN

Speakers:

1. Holly Hinson, MD, MCR, Assistant Professor, Neurocritical Care, Neurology and Emergency Medicine, Oregon Health & Science University, hinson@ohsu.edu
2. Will Meurer, MD, Associate Professor, Departments of Emergency Medicine and Neurology, University of Michigan, wmeurer@med.umich.edu
3. Pooja Khatri, MD, Professor and Director of Acute Stroke Research, Department of Neurology, University of Cincinnati, pooja.khatri@uc.edu
4. Discussants:
 - a. Ed Jauch, MD Professor, Chair - Department of Emergency Medicine, Medical University of South Carolina, jauch@musc.edu
 - b. Irene Ewing, RN, BSN, NIH StrokeNet Project Manager, University of Cincinnati
 - c. Valerie Durkalski-Mauldin, PhD, Professor of Biostatistics, Medical University of South Carolina

Session Type: This session will be structured as a panel consisting of three presentations by academic clinical investigators followed by three discussants who will comment on the challenges of coordinating clinical trials and solutions for success. The speakers' experience will represent a new investigator (early career), a mid-career investigator (serving as PI of one multicenter clinical trial) and a senior investigator (PI or multiple PI of several multi-center clinical trials). Each speaker will share their career path along with their research challenges and successes, particularly in the current practice environment. These presentations will be followed by three discussants who are well-seasoned in conducting/coordinating multicenter clinical trials. They will comment on the speakers' presentations as well as offer key advice for successful trial coordination from a variety of perspectives.

Description: The academic clinical investigator who leads a multicenter clinical trial has a daunting task. Balancing clinical research and clinical duties can be challenging particularly in the current environment of fee-for-service models and relative value units (RVUs). This session will highlight the realities of being an academic clinical investigator and leading a multicenter clinical trial, and the importance of collaboration. Following the presentation from three academic clinical investigators, three discussants representing clinical, biostatistics and project management will comment on the challenges and propose best practices. This will be followed by a panel discussion with a question answer session.

Audience: Although this session highlights the clinical principal investigator, I feel it does have important value to several members of SCT as collaborating colleagues. As a biostatistician, I have noticed a repeating discussion with my clinical collaborators – not enough protected research time to commit to the details of developing and running a multicenter trial. Because the collaboration between the clinical investigator and biostatistician is critical to the success of any trial, I believe biostatisticians (as well as research team members such as project and data managers) would be interested in attending this session to bring information back to clinical colleagues in their research settings.

Contributors

Valerie Durkalski-Mauldin

Holly Hinson

Will Meurer

Pooja Khatri

Ed Jauch

Irene Ewing

Valerie

INVITED SESSION 15 - DYNAMIC AND INTERACTIVE COLLABORATION BETWEEN
QUANTITATIVE AND CLINICAL SCIENTISTS: TOWARDS A BETTER WAY OF MONITORING
AND EVALUATING SAFETY DATA DURING CLINICAL DEVELOPMENT

GREG BALL

Safety monitoring and evaluation of clinical trial safety data requires a partnership between clinical and quantitative scientists. This process is not about testing and confirming. It's an exploratory exercise, for learning and decision-making. Clinicians and statisticians need to collaborate dynamically and interactively together to translate clinical safety questions into useful quantitative frameworks for appropriate application of clinical judgment as opposed to strict statistical inference. Together they can assess the accumulating evidence in the data and drive the clinical decision-making process in a way that encompasses both statistical considerations and medical judgment.

In this session, we will strive to highlight the importance of cross-disciplinary scientific engagement in the development of quantitative procedures for aggregate safety monitoring during clinical development. We propose 1) a multi-disciplinary approach, 2) frameworks around aggregate review and level of evidence and 3) assessments that are product-specific and integrated with medical judgment.

The first speaker will discuss opportunities to enhance cross-disciplinary communication and collaboration in regards to clinical safety data monitoring and assessments. Defining the roles and responsibilities and communication pathways between the different stakeholders involved in clinical trial safety is critical. Ongoing training is important for clinicians and statisticians to have a working knowledge of each other's disciplines and allow a more effective partnership. The vision is to move away from isolated functioning of the disciplines to a more fully integrated approach of quantitative statistical and qualitative clinical assessments.

The second speaker will discuss an interdisciplinary process for the planning and conducting of ongoing aggregate safety evaluations for programs in late stage development (building on the important work from CIOMS VI and the PhRMA SPERT team). Dynamic use of an Aggregate Safety Assessment Plan (ASAP) by multi-disciplinary safety management teams would strengthen cross-disciplinary communication and collaboration for aggregate safety planning and evaluation. An ASAP could be used to coordinate the evolving set of analyses needed to fully characterize the safety profile of the product and to help prepare for safety assessments presented in documents relevant to its safety profile.

The third speaker will discuss the ways in which a statistical reporting group for a Data Monitoring Committee (DMC) can tap into the medical expertise of the Sponsor and the DMC membership itself to help develop the report to the DMC. Discussion with the DMC members can be unfettered because both the reporting group and the DMC should be unblind to study data. Discussion with the Sponsor, on the other hand, must be guarded so as not to jeopardize the integrity of the trial.

Contributors

Greg Ball
Barbara Hendrickson
Greg Ball
Janet Wittes

INVITED SESSION 16 - DEVELOPING A FRAMEWORK FOR THE ETHICAL DESIGN AND
CONDUCT OF PRAGMATIC TRIALS: CONSULTATION WITH THE CLINICAL TRIALS
COMMUNITY

MONICA TALJAARD

Session Description:

In a recently funded four-year project, an international team of ethicists, trialists, methodologists, social scientists, knowledge users and patients aims to develop guidance for the ethical design and conduct of pragmatic randomized controlled trials (pRCTs). In this session, we seek to consult with the clinical trials community about a draft ethics framework to inform the development of guidance. The session is intended to be interactive. A web-based audience response system will be used to allow the audience to participate via the web or SMS texting on their mobile phones. Two recent pRCTs (one conducted in France, one in the USA) will be introduced as case studies. Before and after each presentation, the audience will be invited to vote on the relevance and comprehensiveness of ethical issues identified in the framework.

Talk 1: Introduction [10 min]

Speaker: Jeremy Grimshaw

This talk will introduce pRCTs and provide instruction for audience participation.

Pragmatic RCTs are designed to evaluate treatments in real-world (as opposed to ideal) conditions, directly informing decision-making by patients, providers and healthcare policymakers. The need for more pRCTs is widely recognized. However, pRCTs raise substantial ethical issues that have not yet been adequately addressed. Much of the recent literature on pRCTs appeals to US regulations and lacks convincing arguments grounded in ethical principles. Proposed solutions (e.g. using different regulations in learning healthcare systems) are speculative with no guarantee of improvement over existing oversight procedures. Most importantly, the literature does not reflect a broad vision of protecting core liberty and welfare interests of research participants; novel ethical solutions are required. Until an appropriate ethics framework to address these issues is identified, important research with large potential benefits to patients and healthcare systems may be impeded.

Talk 2: A draft framework for ethical issues in pRCTs [10 min]

Speaker: Charles Weijer

This talk will introduce a new draft ethics framework for analyzing pRCTs. Existing ethical and regulatory frameworks were developed primarily for trials with explanatory aims, i.e. focusing on efficacy of experimental treatments for marketing approval. With the move towards pRCTs, traditional ethics guidance is more difficult to interpret. Challenges arise not only from the pragmatic aims, but are closely tied to study interventions and study design choices. This talk will introduce an initial framework of ethical issues; the pragmatic, intervention and design

characteristics that give rise to these issues; and their implications for researchers and research ethics committees.

Talk 3: The NUTRIREA trial [30 min]

Speakers: Bruno Giraudeau (trialist) and Sarah Edwards (ethicist)

The speakers will introduce the first case, identify specific ethical issues raised and engage in discussion with the audience.

Background: Acute critical illness requiring mechanical ventilation carries a risk of severe malnutrition, which can lead to increased mortality and morbidity. Nutritional support is essential, but the best route of delivery (enteral vs. parenteral) is unclear. While current guidelines recommend early enteral feeding, the quality of evidence underlying these guidelines is low. The NUTRIREA-2 trial was a multicenter parallel arm pRCT at 44 French intensive-care units (ICUs). Adults receiving invasive mechanical ventilation and vasopressor support for shock were randomly assigned to either parenteral nutrition or enteral nutrition within 24 hours after intubation. The primary outcome was mortality at 28 days. There was no significant difference between enteral and parenteral groups with respect to mortality, infectious complications and length of stay; but slightly lower calorie and protein intakes and higher incidence of digestive complications in the enteral group.

This is an example of a pRCT which aims to compare two routinely used treatment strategies with respect to their potential benefits, risks and harms. It is a case that blurs the line between research and clinical practice, as well as challenging traditional approaches to harm-benefit analysis and informed consent. Do patients and clinicians have an obligation to participate in such research? Is patient informed consent required and how much information should be disclosed to patients? Is clinical style consent acceptable? Should drug and non-drug interventions be considered as distinct?

Talk 4: The Flue Vaccine trial [30 min]

Speakers: Monica Taljaard (trialist) and Spencer Hey (ethicist)

The speakers will introduce the second case, identify specific ethical issues raised and engage in discussion with the panel and audience.

Background: Influenza is the most common viral infection affecting older adults. Influenza vaccination is associated with lower rates of hospitalization, deaths and complications in adults over age 50, but influenza severity increases and vaccine effectiveness decreases with age. In 2009, a high-dose influenza vaccine containing four-fold more antigen than the standard dose was licensed by the FDA for individuals older than 65 years. No previous randomized trials have examined clinical effectiveness of vaccines in a nursing home population. A pragmatic cluster randomized trial of 823 US nursing homes and over 50,000 long-stay residents over the age of 65 years was designed to address this question. Nursing homes were randomized to a facility-wide standard of care of either high dose or standard dose vaccine. The primary outcome was hospital admissions related to pulmonary and influenza-like illness. All outcomes were obtained from routinely collected sources. There was a small but statistically significant reduction in the incidence of respiratory-related hospital admissions in the high-dose vaccine arm.

This is an example of a highly pragmatic, cost-efficient trial which compares the population-level impact of two approved vaccines. Cluster randomization substantially simplified the trial logistics: recruitment and randomization of individual residents would have made the trial prohibitively expensive. This case raises ethical questions about which stakeholders have the authority to approve and conduct the trial and the need for additional protections for vulnerable participants. Whose permission is required to conduct the trial? Is cluster randomization with a waiver of resident informed consent justified? What, if any, information should be provided to residents about the trial?

Talk 5: Summary and conclusions [10 min]

Speaker: Dean Fergusson

The final talk will summarize the results of discussion with respect to the comprehensiveness and completeness of the draft framework and consider implications for the guideline development process.

Contributors

Jeremy Grimshaw
Charles Weijer
Spencer Hey
Sarah Edwards
Dean Fergusson
Monica Taljaard
Bruno

INVITED SESSION 17 - ALTERNATIVES TO CONVENTIONAL SURVIVAL ANALYSIS METRICS FOR CLINICAL TRIALS

CHEN HU

Clinical trials remain the fundamental component of modern evidence-based medicine, and evidence demonstrating clinically meaningful benefit of a new treatment regimen from one or more randomized controlled trials (RCT) is essential before its wide adoption. For RCTs with a time-to-event endpoint, which frequently arise in many disease areas such as oncology and cardiology, the log-rank test and Cox proportional hazards model are the “default” analysis methods for statistical inference and for quantifying treatment benefit. However, we have witnessed many challenges and issues when the log-rank test and Cox PH model cannot be readily or properly applied. Moreover, as patients naturally encounter multiple outcomes in their disease course, or are subject to competing risks, there is increasing need and interest in developing and applying alternative metrics and inference tools to assess the benefit-risk profile more efficiently and in a timely fashion. The overarching goal of this invited session is to motivate the need for and describe some recent developments in the use of alternative metrics to evaluate time-to-event data, especially in oncology clinical trials. The following speakers have agreed to present a variety of important topics under this common theme:

- Richard Chappell, PhD, Professor in Biostatistics, University of Wisconsin, Madison.

Dr. Chappell will review and elaborate some criticisms of hazard ratios. For example, a hazard ratio usually lacks an underlying scientific interpretation in medical context, and its estimate can be biased even in the presence of randomization and proportionality. He will also present some alternative measures and discuss their potential use in clinical trials.

- James Dignam, PhD, Professor in Biostatistics, Dept of Public Health Sciences, University of Chicago, IL

Competing risks data are frequently encountered in clinical trials especially in chronic diseases like cancer. For example, individuals undergoing surgical treatment may experience recurrence near the removed tumor, metastatic recurrence at other sites, occurrence of second primary cancer, or death resulting from non-cancer causes before any of these events. In these cases, conventional survival analysis methods fail to reveal a complete picture of the disease and treatment effects. In this talk Dr. Dignam will review the design and analysis aspects of competing risks data, including the use and interpretation of various established methods and some ideas for alternate approaches.

- Masha Kocherginsky, PhD, Associate Professor in Biostatistics, Northwestern University, Chicago, IL.

Dr. Kocherginsky will present a paper on the restricted mean survival time (RMST) and the impact of covariate adjustment. Because estimation of RMST adjusted for covariates is based on a model non-linear in the covariates, it is not straightforward but important to investigate whether the comparison of RMSTs with adjustment for covariates improves precision of the estimated treatment effect (difference in RMSTs between treatment arms), compared to the unadjusted estimator. She will discuss various ways to interpret the restricted mean, as well as the extent to

which adjustment for covariates provides an improvement in the precision of the estimated treatment effect.

- Chen Hu, PhD, Assistant Professor in Oncology Biostatistics, Johns Hopkins University School of Medicine, Baltimore, MD.

Dr. Hu will present a novel summary metric for benefit-risk assessment, which incorporates a longitudinal marker process and a terminal event, and discuss its potential use in the context of oncology clinical trials. This work aims to provide a useful tool to address a long-standing challenge in medical decision making process. Conventionally when the treatment effects on both of a longitudinal marker process and a terminal event are both of particular interest, the decision making process largely rely on qualitatively integrating the segregated efficacy evaluations based on each endpoint. The proposed summary measure allows one to quantitatively integrate information from both endpoints such that the decision making may reply on comparing the summary measure between treatment arms directly. He will focus on its particular application in oncology trial design and analysis.

Contributors

Chen Hu
Richard Chappell
James Dignam
Masha Kocherginsky
Chen Hu

INVITED SESSION 18 - OPTIMIZING INVESTIGATIONAL DRUG MANAGEMENT TO
ENHANCE CLINICAL TRIAL OPERATION QUALITY

CATHERINE DILLON

Study drug management is a complex and critical component of clinical research. Per federal regulations, investigational drug must be accounted for at all times and failure to do so can negatively impact the validity of the study's results. Potential risks associated with inadequate study drug management include treatment cross-overs, bias introduced by failure to blind, and insufficient site inventory of drug. Simply maintaining drug accountability is not enough and study teams should implement proactive QA/QC procedures which target critical risks into their investigational drug plans.

An Automated Drug Distribution and Tracking module integrated within a CTMS can provide full scope accountability from drug packaging at the central pharmacy to removal from site inventory. QA/QC strategies can be implemented for each step of the accountability process including lot registration, shipping path definition, label printing, kit packing, drug request, drug shipping, drug receiving, drug assignment, drug damage, and drug expiration.

It's imperative that study drug is easily accessible on site and matches the randomized treatment assignment, but cost must be balanced against waste. In order to determine an appropriate site inventory of study drug expiration dates, recruitment rates, sample size, randomization ratios, and pharmacy space must be considered. Response-adaptive randomization trials have become more popular in recent years with expected benefits in trial efficiency and subject ethics. However, these types of studies create special challenges in ensuring study drug availability at the time of randomization.

Novel study drug management techniques have been implemented for a variety of clinical trials at the Data Coordination Unit. As case examples two currently enrolling trials will be reviewed:

1) ESETT is a randomized, multicenter, Bayesian response adaptive trial of three active treatments in patients with status epilepticus. 795 subjects at 60 sites will be randomized, stratified by 3 age groups. Dynamic randomization ratios, stratification of randomization by age, and the emergency setting created special challenges in ensuring the proper treatment assignment was on site at the time of randomization.

2) ARCADIA is a multicenter, randomized, phase 3 clinical trial of apixaban versus aspirin to assess recurrent stroke-free survival time. 1,100 subjects at 120 sites will be randomized 1:1 to receive either apixaban or aspirin for up to 4 years. As only a 90 supply of study drug can be dispensed and subjects may switch from regular dose to low dose apixaban during the course of the trial, a plan ensuring the resupply drug matches the original treatment assignment and the appropriate dose was developed.

Speakers:

- Wenle Zhao will discuss the challenges of study drug management.

- Keith Pauls will discuss building QA/QC into a drug tracking module within an integrated CTMS.
- Caitlyn Meinzer will discuss study drug inventory management.
- Catherine Dillon will provide real trial examples of novel study drug management plans.

Contributors

Catherine Dillon
Wenle Zhao
Keith Pauls
Caitlyn Meinzer
Catherine Dillon

INVITED SESSION 19 - INCLUDING PREGNANT AND LACTATING WOMEN IN CLINICAL TRIALS: CONTROVERSIES, CHALLENGES AND OPPORTUNITIES

PAMELA SCOTT

Theme: Pregnant and Lactating Women in Clinical Trials

Purpose: There are very few prescription medications that have been specifically approved for use during pregnancy or lactation. However, doctors in clinical practice must prescribe needed medicines to pregnant and lactating women to treat a variety of illnesses and conditions such as diabetes, high blood pressure or even something as simple as a dental infection.

Clinical trials are important to understanding the safety and efficacy of medical products on the user population, yet there are very few clinical trials that test the safety of these products during pregnancy or lactation due to concerns about the health of the mother and child. More information is clearly needed about safety and efficacy of medical products for pregnant and lactating women.

The purpose of this panel is to discuss the ethical challenges yet critical need for the consideration of pregnant and lactating women in clinical trials.

5 speakers (10-15 minutes each)

Proposed schedule:

1.) Moderator/ Speaker 1 (10 minutes) –Marjorie R. Jenkins, MD, MEdHP, FACP

- Presentation topic: Update on FDA Activities Related to Pregnant and Lactating Women
- Abstract: Clinical trials are important to understanding the safety and efficacy of medical products on the user population, yet there are very few clinical trials that test the safety of these products during pregnancy or lactation due to concerns about the health of the mother and child. More information is needed about safety and efficacy of medical products for pregnant and lactating women. The 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to provide recommendations to the Secretary of Health and Human Services on how to improve the development of safe and effective therapies for pregnant women and nursing mothers, as well as guidance on how to best collaborate and coordinate these activities at the federal level. PRGLAC will also plan ways to effectively communicate research findings and other pertinent information to health care providers and the public. This presentation will provide an overview of the above issues and set the stage for a robust panel discussion.

2.) Speaker 2 (15 minutes) – Karim Calis, PharmD, MPH, FASHP, FCCP

- Presentation topic: IRB Interpretation of 45 CFR 46 Subpart B
- Abstract: Study risks and benefits for pregnant women must be carefully interpreted in the context of the specific medical condition under study. Nonetheless, IRBs may vary in their interpretation of regulations governing clinical research and in their assessment of research-

related risks and benefits. The assessment of risk is particularly complex for research involving investigational products because of the limited human exposure data and the interdependence of maternal and fetal health and welfare. The IRB has an ethical imperative to safeguard and protect the interests of all research participants while also ensuring that pregnant women are not unjustifiably excluded from clinical research. This presentation will discuss IRB considerations pertaining to the inclusion of pregnant women and lactating women in clinical trials.

3.) Speaker 3 (15 minutes) – Kevin Prohaska, D.O., M.P.H., Captain (USPHS)

- Presentation topic: Ethical Considerations Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Trials: FDA Perspective
- Abstract: The inclusion of pregnant women in clinical research can raise complex ethical issues. The ethical complexity stems from the necessity to balance the interest of the pregnant woman and the fetus with the needs of the research plan. This session will provide an FDA perspective of the issue, addressing the FDA specific regulations and policies regarding the inclusion of pregnant and lactating women. Ethical considerations and implications of including and not including pregnant women in research will be discussed. These include but are not limited to the risks of fetal exposure and limitations in therapies that have not been studied in pregnant and lactating women.

4.) Speaker 4 (15 minutes) – Christina Bucci-Rechtweg, MD

- Presentation topic: Challenges Within Industry for the Inclusion of Pregnant and Lactating Women in Clinical Trials
- Abstract: This presentation will provide an industry perspective on the inclusion of pregnant and lactating women in drug development trials. A review of the inclusion of pregnant and lactating women in industry-sponsored clinical trials will be provided. Current complexities hindering inclusion of pregnant and lactating women, and the activities approaches, and opportunities in industry for including pregnant and lactating women will be discussed.

5.) Speaker 5 (15 minutes): -- Anne Lyerly, MD, MA

- Presentation topic: The Dilemma of Providing Pregnant and Lactating Women with the Best Possible Care: Ethics, Research and Clinical Care
- Abstract: Few prescription medications have been specifically approved for use during pregnancy. And yet, medications are taken by women as prescribed by a health professional as necessary to treat a variety of illnesses and conditions (e.g., diabetes, high blood pressure) during pregnancy, as well as before the woman is aware of her pregnancy. This presentation will discuss the dilemma of prescribing drugs for pregnant and lactating women within the context of limited safety information and its ethical implications related to the inclusion of pregnant and lactating women in clinical trials from the perspective of an obstetrician/gynecologist.

Moderated Q&A – (20 minutes)

Total time: 90 minutes (1 hour and 30 minutes)

Contributors

Pamela Scott

Marjorie Jenkins

Karim Calis

Kevin Prohaska

Christina Bucci-Rechtweg

Anne Lyerly

INVITED SESSION 20 - IN MEMORY OF DAVE SACKETT: INTERIM DATA SHARING BY DATA SAFETY MONITORING BOARDS OF TRIALS (ALTERNATIVE TITLE: DAVE SACKETT'S LAST PROJECT ON INTERIM DATA SHARING BY DSMBS OF TRIALS)

LEHANA THABANE

Dave Sackett dedicated most of his career on improving patient outcomes through the conduct of high quality trials including systematic synthesis of evidence from trials to inform clinical decision-making. One of his last projects focused on sharing of interim results by the DSMBs with non-DSMB trial stakeholders including principal investigators, sponsors and the steering committee—because this is an important issue that can affect trial integrity. Typically, such stakeholders do not see the interim data while the trial is still in progress. However, in some instances such stakeholders have asked for or feel a need to see interim data or statistical extrapolations from interim data. This session will address the following questions: 1) Should DSMBs share interim data (or statistical extrapolations from those data) with investigators, sponsors, or steering committees during the conduct of an RCT? If the answer is no, why should DSMBs not share interim data or extrapolations from the data?; 2) If yes, what type of interim data or statistical extrapolations should the DSMB communicate and with whom should they communicate the information?; and 3) What is the rationale behind sharing a certain piece of interim information, and how can that help or harm the successful conduct and definitive completion of the trial?

This 90-minute session will briefly refresh memories on the role of DSMBs in trials; what interim data (or statistical extrapolations from those data) can be shared by DSMBs, and with examples where some of these had been shared leading to concerns about how those receiving the information might use the data.

Suggested organizers, chair, speakers and discussant:

10 minutes from the Chair: Lehana Thabane (who will open by refreshing memories with Dave's perspective on the issues)

20 minutes from Someone who has substantial experience serving on DSMBs and has written widely about DSMB issues: Tom Fleming (PhD) Professor of the Department of Biostatistics, and co-author of: *Data Monitoring Committees in Clinical Trials: A Practical Perspective*. Wiley & Sons, 2002.

Title: Maintaining confidentiality of emerging data and the independence of DSMBs

Abstract: Dr Fleming will describe the best practices of considerable importance to the ability of DSMBs to achieve their mission of safeguarding the interests of trial participants and enhancing the integrity and credibility of trials. His talk will specifically address issues of maintaining confidentiality of emerging data, and why such data should be shared on a limited “need to know” basis relating to the ability to carry out ethical or scientific responsibilities in the conduct of the trial.

20 minutes from Someone who has substantial experience serving on advisory committees, and DSMBs for trials with industry or government sponsors: Janet Wittes (PhD). Founder, Statistics Collaborative, Inc. (SCI), and author of many papers on DSMBs.

Title: Best practices in data sharing by DSMBs: lessons from serving on DSMBs of industry and government sponsored trials

Abstract: In this presentation, Dr Wittes will share her experiences as a DSMB member of several trials sponsored by both industry and government, where some need to share interim results occurred. Her talk will focus on lessons learnt and how such lessons can lead to best practices.

20 minutes from a graduate student who has conducted a survey designed with Dave Sackett: Victoria Borg Debono (PhD student), at McMaster University, and coauthor of two papers on the topic (Trials 2017; 18:120; and Contemporary Clinical Trials Communications 2017;81-85).

Title: Results of a 2015 survey of the views of SCT and ISCB members on interim data sharing by DSMBs: what to share, with whom, and why?

Abstract: This talk, Victoria will describe the results of an online survey of members of the Society of Clinical Trials (SCT) and International Society of Clinical Biostatistics (ISCB) in 2015 asking their professional views on sharing interim results.

20 minutes for Summary and open discussion, chaired by: Lehana Thabane

Special Request: All three invited speakers have agreed to take part in the session. However, Dr Tom Fleming has teaching commitments and has asked that we make a special request for the session to be scheduled (in order of preference):

1) on May 22, 2018; or

2) after 2pm on May 21 or 23.

If at all possible, the first option was the most preferred by all speakers.

Contributors

Lehana Thabane

Tom Fleming

Janet Wittes

Victoria Borg Debono

INVITED SESSION 21 - DESIGN OF AN ADAPTIVE TRIAL OF EXTRA-CORPOREAL
MEMBRANE OXYGENATION FOR REFRACTORY OUT-OF-HOSPITAL CARDIAC ARREST
(EROCA)

JULIANA TOLLES

Brief Overview: This session will focus on the trial design and implementation challenges of an adaptive trial of Extra-Corporeal Membrane Oxygenation for Refractory Out-of-hospital Cardiac Arrest (EROCA). The speakers will discuss challenges and design solutions in trial implementation, statistical methodology, and ethical conduct of the trial. This topic is especially timely in light of the May 2017 presentation of the successful DAWN trial for endovascular therapy in stroke, which effectively implemented an adaptive enrichment design and has generated renewed interest in this innovative type of trial.

Titles of talks:

1. Clinical Question: ECMO for Out-of-Hospital Cardiac Arrest – Will Meurer, MD MS

Extracorporeal life support is a potentially life-saving therapy for cardiac arrest victims but is very expensive and resource intensive. Additionally, it must be initiated very early after the onset of cardiac arrest in order to minimize brain ischemia. In this session, Dr. Meurer (an emergency physician and clinical trialist) will describe the clinical goals of randomized trials in this area. The overarching question is how soon after cardiac arrest patients need to be started on ECMO in order to have a reasonable chance of neurological recovery.

2. Pilot Trial Design – Will Meurer, MD MS

The National Heart Lung and Blood Institute funded the EROCA pilot trial. Dr. Meurer will describe the procedures for randomization in the field, the overall aims, and the progress of the study so far.

3. Adaptive Enrichment Trial Design and Simulation – Juliana Tolles, MD, MHS

(with content contribution from Kelley Kidwell, PhD)

The future, pivotal EROCA trial will incorporate enrichment into the design. The time window for enrollment eligibility after cardiac arrest will be adaptively expanded or contracted based on analysis of outcomes at predetermined interims using prospectively defined decision criteria. Extensive simulations are required both to select optimal parameters and to predict the statistical behavior of this adaptive design. Dr. Tolles will discuss the concept and preliminary results of simulations from this part of the project.

4. Ethical Challenges in Clinical Trials for Emergent Conditions - Dixie Ecklund

Ms. Ecklund will provide reflections on the operational and ethical aspects of emergency trials in general and the EROCA trial in particular.

5. Discussion and Comment - Leslie McClure, PhD

Dr. McClure will provide discussion points from the talks and a framework of future considerations for the design of adaptive clinical trials in emergencies. She will lead a panel discussion and solicit ideas, questions, and feedback from the audience.

Contributors

Roger Lewis
Will Meurer
Will Meurer
Juliana Tolles
Dixie Ecklund
Leslie McClure

INVITED SESSION 22 - DYNAMIC DETERMINATION OF A POWER PRIOR PARAMETER –
THE DISCOUNT PRIOR APPROACH

THEODORE LYSTIG

The Medical Device Innovation Consortium (MDIC) is a public-private partnership created with the sole objective of advancing medical device regulatory science. Recently, the Virtual Patients working group at MDIC has developed a promising new approach for the synthesis of historical and current information when there is skepticism about the relevance of the historical data to the current data. This setting is of relevance to medical device studies as while there frequently exists data from predicate devices it is often unclear how closely the performance of a new device will track the performance of an earlier version of the product. In addition to medical devices, the methods discussed in this session have a natural extension to settings such as rare diseases, pediatric applications, and oncology (all of which tend to have multiple small studies as opposed to large, definitive studies).

Often, informative priors will be used in Bayesian analyses to quantify prior knowledge for a product under study. When the prior information closely aligns with the new information, the safety and efficacy of products can be demonstrated more quickly than if such prior information was ignored. A power prior model formulation is a popular means of combining data sources with reasonable similarity. However, there exists the possibility that the historical and current studies will have markedly different behavior, calling into question the appropriateness of blending conflicting data in the analysis. The MDIC working group has developed a new method which builds on the existing power prior framework by introducing a discounting function that alters the extent to which historical information influences the analysis, modifying the value of the power parameter in direct proportion to the measure of agreement between the historical and the current data.

This invited session will present an overview and discussion of the latest developments for the discount prior approach. Dr. Dawn Bardot will begin the session with an introduction to MDIC and a presentation of how the discount prior project has evolved, including the active partnerships that have contributed to its success. Dr. Laura Thompson will give an overview of the theoretical framework, as well as outlining aspects of the approach that are of interest to the FDA as a regulatory agency. Mr. Tarek Haddad will present a range of simulations to examine the operating characteristics of the approach, and will also provide an example of the approach applied in a re-analysis of a well-known medical device trial. Dr. Jason Connor, a frequent participant in FDA Advisory Panels, will provide his view on potential remaining challenges prior to the method being well received beyond sponsors and regulators. The session will conclude with a moderated panel discussion that will solicit feedback from the audience. All speakers are confirmed.

Contributors

Theodore Lystig
Dawn Bardot
Laura Thompson
Tarek Haddad
Jason Connor

INVITED SESSION 23 - ACHIEVING THE IMPOSSIBLE? CASE STUDIES OF SUCCESSFUL RECRUITMENT TO RANDOMISED CLINICAL TRIALS CONSIDERED CONTENTIOUS OR IMPOSSIBLE

NICOLA MILLS

SESSION OVERVIEW

Recruitment to randomised clinical trials (RCTs) is often challenging. Recruitment to controversial Phase III RCTs with very different interventions has sometimes been considered “impossible”. Although recruitment difficulties are often perceived to arise from practical, logistical and patient related issues, recent evidence suggests these may also reflect recruiters’ underlying discomforts with fundamental aspects of the design of clinical trials and/or their dual clinical and research roles.

In this session we present case studies of recruitment to challenging Phase III RCTs in surgery, oncology and associated specialities. Each RCT included a QRI - QuinteT (Qualitative Research integrated within Trials) Recruitment Intervention. The QRI is a flexible intervention that has been embedded within over 25 feasibility and major RCTs to understand and address recruitment challenges.

Through these case studies of RCTs comparing very different interventions, or interventions that are expected to provoke strong patient and clinician preferences, we identify generic and trial-specific barriers to recruitment. The novelty of the QRI lies in its ability to uncover hidden emotional and intellectual challenges faced by recruiters and then develop strategies to overcome them. Through a panel and open discussion, we aim to encourage the audience to consider the challenges of recruitment in their experience and whether this approach is best focused on particular clinical trials or has wider applicability.

PRESENTATIONS

1. Introducing the QuinteT Recruitment Intervention (QRI) (Dr Nicola Mills)

Scene setting with an overview of the challenges of recruitment to RCTs and the QuinteT Recruitment Intervention designed to address them.

2. Presentations of examples of recruitment difficulties and solutions in RCTs deemed difficult, contentious or impossible:

- RCTs comparing radical with conservative interventions for cancer using evidence from the ProtecT RCT (Professor Jenny Donovan)

This presentation will consider the challenges of recruitment to RCTs in cancer where treatment options are very different. It will draw on evidence from the ProtecT RCT evaluating the effectiveness of radical surgery, radiotherapy and active monitoring for localised prostate cancer. The ProtecT RCT recruited over 1600 participants to random treatment allocation.

- RCTs comparing very different types of surgical procedures using evidence from the ROMIO and By-Band-Sleeve RCTs (Professor Jane Blazeby)

In this talk, the particular challenges of recruiting to RCTs involving surgical interventions will be highlighted, with examples offered of how they can be minimised. Data will be drawn from two surgical RCTs, both of which recruited to target early in the feasibility stage and progressed to a main RCT that is still ongoing - ROMIO evaluating the effectiveness of minimally invasive and open surgical procedures for esophageal cancer, and By-Band-Sleeve comparing gastric bypass, gastric band and sleeve gastrectomy for severe and complex obesity.

- RCTs comparing surgery with placebo/sham surgery and no treatment, using evidence from the CSAW study (Professor David Beard)

Placebo/sham-controlled RCTs of surgery have many challenges. Drawing on evidence from an RCT of surgery, sham surgery and no treatment for subacromial shoulder pain that completed recruitment and recently published its outcomes (CSAW RCT), we explore recruitment issues inherent in such clinical trials.

PANEL AND OPEN DISCUSSION

Interactive discussion to consider the challenges of recruitment to 'difficult' RCTs and whether the QRI identifies key challenges that are specific to such RCTs, or has broader applicability to RCTs of greater or lesser complexity, and in different contexts.

Contributors

Nicola Mills
Nicola Mills
Jenny Donovan
Jane Blazeby
David Beard

INVITED SESSION 24 - WHEN PRAGMATISM AND REALITY COLLIDE: USE OF THE PRECIS
1 AND 2 TOOLS IN PCORI FUNDED TRIALS

MERRICK ZWARENSTEIN

Background:

Over the last decade concern has risen among patients, clinicians and health system managers and funders over the relevance of randomized controlled trial results to the real world decisions they must make every day.

In 1967, Schwartz and Lellouch, two French statisticians distinguished trials aimed at confirming a mechanism of action of an intervention (an explanatory attitude), from those aimed at assisting decision-makers to choose between alternative interventions for care (a pragmatic attitude). In 2009 we developed, and in 2015 updated the PRECIS (Pragmatic Explanatory Continuum Indicator Summary) tool, a 9 domain scoring wheel with a narrative scoring guide to help designers of randomized trials to make nine decisions, each tuning an aspect of trial design to their intended attitude between very pragmatic and very explanatory.

PCORI has distributed over \$1 billion towards real world comparative effectiveness evaluations of alternative interventions, mainly randomized trials. The calls for some of these competitions, resulting in nearly 100 trials, have strongly encouraged that applicants take a more pragmatic approach by explicitly referencing the PRECIS papers as a guide to pragmatic trial design, but have not mandated specific design choices.

This natural experiment is an opportunity to describe examples from a large body of trial designs in relation to the PRECIS 2 wheel, in order to reveal investigators understanding of and response to PRECIS, and to identify real world constraints on pragmatic design choices.

Pcori staff will describe their intent in establishing their Pragmatic Clinical Studies funding program, and brief outlines of the number and types of awards to date. Three PCORI-funded scientists will describe their trials, and their decision process and use of the PRECIS tool, and the designers of the PRECIS 2 tools will indicate areas where a designers of the PRECIS tools might respond to the lessons of this large body of trials with changes to future iterations. This will be followed by panel and plenary discussion.

1. Introduction of session and panel by Chair: Merrick Zwarenstein 5 minutes

2. Summary information about the PCORI Portfolio of pragmatic clinical studies will be provide by Anne Trontell from the PCORI Science Office and who aids in the oversight of these studies. 15 minutes

"Pragmatic Clinical Trials: PCORI and PRECIS Perspectives" will describe the portfolio, survey results of PCORI investigators of PRECIS domains that are problematic to implement with examples.

Anne Trontell, MD, MPH

Associate Director, Clinical Effectiveness and Decision Science

PCORI

3. Three PCORI-funded principal investigators will be invited to speak for ~15 min each about 2 -3 design choices they made to address their real-world comparative effectiveness question with as pragmatic a design as possible. Tentatively scheduled are the following:

3.1 "Anti-TNF Monotherapy versus Combination Therapy with Low Dose Methotrexate in Pediatric Crohn's Disease" (a double-blind, placebo-controlled pragmatic trial) 15 min

Michael Kappelman, MD, MPH

Professor of Pediatrics and Epidemiology

University of North Carolina at Chapel Hill

3.2 "PREPARE Study: Real Life vs. Real Life" (a study of as-needed controller use during asthma exacerbations where the combination inhaler is not yet available, addressing issues of design for a future state) 15 min

Elliot Israel, MD

Professor, Harvard Medical School

Director of Clinical Research, Pulmonary and Critical Care Division,

Brigham & Women's Hospital

3.3 "Applying the PRECIS criteria in practice: experiences from REGAIN" (a study of two anesthetic choices in hip fracture surgery and managing individual practitioner practice variation and other challenges) 15 min

Mark D. Neuman, MD, MSc

Assistant Professor of Anesthesiology & Critical Care

University of Pennsylvania

4. Serving as a discussant of the presentations and their implications for refinement and modification of PRECIS will be one of the authors of PRECIS and PRECIS 2, Merrick Zwarenstein. 15 min

Merrick Zwarenstein, MBBCh, MSc, PhD

Director of the Centre for Studies in Family Medicine, Department of Family Medicine

Western University

London, Ontario

5. Panel Discussion 15 min

6. Plenary Discussion 15 min

Contributors

Merrick Zwarenstein

Anne Trontell

Kirsty Loudon

Shaun Treweek

Sean Tunis

INVITED SESSION 25 - ROLE OF DATA MONITORING COMMITTEES IN COMPLICATED TRIALS

SUSAN HALABI

The primary role of the Data Monitoring Committee (DMC) is to ensure the overall safety of participants, and to make sure that the trials are conducted with both scientific rigor and the highest ethical standards. Most randomized clinical trials include strategies for terminating early if a treatment arm is found to be either effective or harmful to the patients. Members of the DMC usually rely on stopping guidelines such as group sequential design (GSD) to minimize the role of subjective judgment. Although GSDs serve as an aid in monitoring throughout the trial, they do not sufficiently take into account all of the complex factors in a reasoned decision to stop a trial early. Scientific information external or internal to the trial may suggest that patients with certain biomarkers/attributes may benefit from the investigational agent(s), whereas the control may not. Another common challenge is that at an interim analysis the data may show that the biomarker/attribute prevalence is less than expected and that the actual treatment benefit is smaller than the hypothesized treatment benefit and that the trial may need to be re-sized. One key issue to consider is how to integrate evolving information during the monitoring process. If changes to the trial are to be implemented, the challenge is to minimize operational biases that can adversely affect the validity of a trial. Multiple considerations in the decision to stop a trial (or an arm of a trial) in addition to using statistical monitoring guidelines will be evaluated. A well-appointed DMC may be in a unique position to advise the sponsor and save a trial. In this session, three lead statisticians and a clinician from academia will present their perspectives on the challenges of monitoring complicated trials. In addition, the risks and potential consequences of terminating a trial early will be discussed with an emphasis on statistical issues related to the estimation of the treatment effect and the analysis and interpretation of the primary and secondary endpoints. Several examples of complicated trials in cardiovascular trials, women's health initiative and oncology trials will be discussed.

Format of session: 4 speakers followed by Q&A, each talk will be for 18 minutes and 18 minutes for Q and A. All speakers are available and accepted to be part of the session. Dr. Garnet Anderson is available after Monday May 21, 2018.

Speakers:

Barry Davis, M.D., Ph.D., University of Texas Health Sciences Center at Houston, TX

Title: Challenges in Monitoring Large Cardiovascular Trials

Garnet Anderson, Ph.D. (Available after Monday May 21, 2018)

Fred Hutchinson Cancer Center, Seattle, WA

Title: Challenges of monitoring multiple endpoints: The Women's Health Initiative example

Susan Halabi, Ph.D.

Duke University

Title: Group Sequential Implementation in Oncology: Uses and Abuses

Oliver Sartor, M.D.

Tulane University, New Orleans, LA

Title: DMC Decision Making: Problems And Pitfalls

Contributors

Simon Day

Barry Davis

Garnet Anderson

Susan Halabi

Oliver Sartor

INVITED SESSION 26 - PHASE 2 BASKET TRIAL DESIGNS AND APPLICATIONS

MITHAT GONEN

Current oncology drug development primarily focuses on therapies that are mechanistically designed to work against tumors harboring specific molecular aberrations. Due to rapid advances in genomic sequencing and technology, investigators have found these specific mutational targets typically occur in only a small proportion of tumors but also tend to be present in many tumor types. This has led to a growing interest in a class of designs called “basket trials”, whereby treatment allocation is biomarker-driven rather than disease-driven. In these studies, investigators are essentially screening for specific populations that respond to the drug. Consequently, there are many inherent complexities in the design and implementation of such trials. The goal of this session is to bring researchers together to present and discuss their work and clinical experience in this developing field. Speakers and their abstracts are given below

Speakers:

Speaker 1: Renfro, Lindsay A., Ph.D.

Associate Professor of Biostatistics, Mayo Clinic, Division of Biomedical Statistics and Informatics

[Renfro.Lindsay@mayo.edu]

Title: Basket trials: features, examples, and challenges

Abstract: Lindsay Renfro will introduce basket trials, describing definitions, motivation for use, unique features, and real-world examples. She will also emphasize practical and statistical challenges that often occur during their implementation.

Speaker 2: Kristen Cunanan, PhD

Research Scholar

Department of Epidemiology and Biostatistics

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Title: Evaluating the statistical properties of Bayesian basket trial designs

Depending on previous regulatory approval in other disease indications, investigators may be inclined to expect broad efficacy across all baskets at the onset of a basket trial. Bayesian modeling is an appealing approach for a basket trial design to capitalize on the expected correlated efficacies between baskets and potentially improve power and trial efficiency, as compared to say independent designs run in parallel for each basket. Both designs using Bayesian hierarchical modeling and mixture modeling have been proposed. In preliminary work, we have found in simple settings there is little performance improvement by introducing such modeling complexity

of multiple mixtures. In this talk we present our findings from the investigation of potential gains of such complexities and when they are needed.

Speaker 3: Brian P. Hobbs

Cleveland Clinic Foundation

Hobbs,Brian Paul 'bphobbs@gmail.com'

Title: Bayesian Basket Trial Design with Exchangeability Monitoring

Abstract: Precision medicine endeavors to conform therapeutic interventions to the individuals being treated. Implicit to the concept of precision medicine is heterogeneity of treatment benefit among patients and patient subpopulations. Thus, precision medicine challenges conventional paradigms of clinical translational which have relied on estimates of population-averaged effects to guide clinical practice. Basket trials comprise a class of experimental designs that endeavor to test the effectiveness of a therapeutic strategy among patients defined by the presence of a particular biomarker target (often a molecular feature) rather than a particular cancer type. Acknowledging the potential for differential effectiveness on the basis of traditional criteria for cancer subtyping, evaluations of treatment effectiveness are conducted with respect to the "baskets" which collectively represent a partition of the targeted patient population consisting of discrete subtypes. Yet, designs of early basket trials have been criticized for their reliance on basketwise analysis strategies which suffered from limited power in the presence of imbalanced enrollment as well as failed to convey to the clinical community evidentiary measures for consistent effectiveness among the studied clinical subtypes. This article presents novel methodology for sequential basket trial design formulated with Bayesian monitoring rules with interim analyses based a novel hierarchical modeling strategy for sharing information among a collection of discrete, potentially non-exchangeable subtypes. The methodology is demonstrated with both analysis and permutation studies based on data reported from a recent basket trial designed to estimate the effectiveness of vemurafenib in BRAFV600 mutant non-melanoma among six clinical sites.

Speaker 4

Rong Liu, PhD

Rong Liu [rong.liu@bayer.com]

Deputy Director, Principle Statistician, Bayer Health Group

Title: Increasing the efficiency of oncology basket trials using a Bayesian approach

Abstract:

With the rapid growth of targeted and immune-oncology therapies, novel statistical design approaches are needed to increase the flexibility and efficiency of early phase oncology trials.

Basket trials enroll patients with defined biological deficiencies, but with multiple histologic tumor types (or indications), to discover in which indications the drug is active. In such designs different indications are typically analyzed independently. This, however, ignores potential biological similarities among the indications. Our research provides a statistical methodology to enhance such basket trials by assessing the homogeneity of the response rates among indications at an interim

analysis, and applying a Bayesian hierarchical modeling approach in the second stage if the efficacy is deemed reasonably homogenous across indications. This increases the power of the study by allowing indications with similar response rates to borrow information from each other. Via simulations, we quantify the efficiency gain of our proposed approach relative to the conventional parallel approach. The operating characteristics of our method depend on the similarity of the response rates between the different indications. If the response rates are comparable in most or all indications after treatment with the investigational drug, a substantial increase in efficiency as compared to the conventional approach can be obtained as fewer patients are required or a higher power is attained. We also demonstrate that efficacy again decreases if the response rates vary considerably among tumor types but it is still better than the conventional approach.

Contributors

Alexia Iasonos
Lindsay Renfro
Kristen Cunanan
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Rong Liu

INVITED SESSION 27 - PRAGMATIC BENEFIT:RISK ASSESSMENT IN CLINICAL TRIALS: A
NEW PARADIGM USING PAIRWISE COMPARISON OF PATIENTS

SCOTT RICHARD EVANS

An ultimate goal of many clinical trials is to contrast the benefits and harms of alternative therapies to help inform clinical decision-making. Typically a treatment effect on each outcome of interest is estimated and these effects are combined formally or informally as part of a benefit:risk analysis. However benefit:risk assessment based on combining the separate marginal effects on each outcome carries several limitations. These include: failure to address the most relevant clinical question regarding the global assessment of the effects on patients, evaluating efficacy and safety in different populations challenging the interpretation of generalizability, failure to incorporate the association between outcomes, and lack of assessment of the cumulative or nature of events or the competing risk nature of events. Evolving approaches based on pairwise comparisons of patients between randomized treatment arms, provide a quantitative global assessment that addresses these challenges. The concept uses the outcomes to analyze patients rather than patients to analyze outcomes, accommodating several outcomes with differential importance. Ranking global patient outcomes provides a more clinically relevant evaluation to inform clinical decision-making than combining separate marginal effects.

Speaker titles and bios are below.

Marc Buyse

Title: Generalized pairwise comparisons for personalized medicine

Bio: Marc Buyse holds a ScD in biostatistics from the Harvard School of Public Health (Boston, MA). He worked at the EORTC in Brussels and at the Dana Farber Cancer Institute in Boston. He is founder and Chief Scientific Officer of the International Drug Development Institute (IDDI) and of CluePoints.

Abstract: Generalized pairwise comparisons extend the Mann-Whitney form of Wilcoxon's test. The test uses all pairwise comparisons between two patients in different treatment arms in terms of one or several prioritized outcomes. The "net treatment benefit" is the difference between the proportion of pairs in favor of treatment less the proportion in favor of control. A similar approach led to the "win ratio", the proportion of pairs in favor of treatment over the proportion of pairs in favor of control. For one variable, the net treatment benefit has a simple relationship with traditional measures. Pairwise comparisons can incorporate thresholds of clinical relevance, enable several outcomes to be analyzed simultaneously, and can be used flexibly for the benefit risk assessment of therapeutic interventions.

Julien Peron

Title: Analyses of times to event and multiple outcomes in randomized trials using generalized pairwise comparisons

Bio: Julien Péron holds a PhD in biostatistics from the Lyon 1 University (France). He also holds a MD in medical oncology from the same university. He practices medical oncology in the Centre Hospitalier Lyon Sud, Lyon, France, and currently works at the EORTC in Brussels as a medical fellow.

Abstract: Generalized pairwise can be used to estimate the net benefit of interventions assessed in randomized trials. The method can incorporate thresholds of clinical relevance if a single time-to-event outcome is of interest and incorporate multiple outcomes in a single analysis. The advantages and limitations of generalized pairwise comparisons will be illustrated: (1) For a single time-to-event endpoint, the net survival benefit is a meaningful measure of treatment effect whether or not hazards are proportional. When a delayed treatment effect is anticipated, the net benefit is appealing because it stresses benefits that are clinically worthwhile on the time scale. The test can gain power as compared to the logrank test if interest focuses on long-term survival differences. (2) Anticancer treatments have toxicities that may counterbalance treatment benefits. Generalized pairwise comparisons can be used to assess the benefit-risk balance of new treatments. This will be illustrated using trials in patients with metastatic pancreatic cancer.

Dean Follmann (dfollmann@niaid.nih.gov)

Title: A semiparametric regression approach for ordered composite endpoints in clinical trials with censoring

Bio: Dean Follmann is the head of the Biostatistics Research Branch at the National Institute of Allergy and Infectious Diseases. He is a Fellow of the American Statistical Association and has interests in infectious diseases, clinical trials, and statistical methodology.

Abstract: Composite endpoints are frequently used in clinical trials when a single endpoint is rare or insufficient to characterize the course of a disease. In cardiovascular disease the composite endpoint might include death, stroke, myocardial infarction, or revascularization. Often, components of the endpoint are treated equally, for example, by using the time to occurrence of the first of any constituent endpoints. Different researches have sought to reflect the natural rank of the composites through an ordinal outcome. If all patients are followed for the same amount of time then ranking by the desirability of the outcome (DOOR) is relatively straightforward but more complicated with censoring. Methods have typically been restricted to the two group setting and incorporation of covariates is unclear. We show how an ordering score can be defined to operationalize the ranking rule and how the ordering score can be used to estimate different estimands, e.g. DOOR and win ratio, with censored data by repurposing standard software. We assume the ordering score, is transformable to an exponential random variable to incorporate covariates. This results in a semi-parametric model equivalent to a proportional hazards model with multiple interval censoring. The model can be fit using standard Cox regression software following creation of a specialized dataset. The methods are applied to a clinical trial with an ordered outcome.

Scott Evans (evans@sdac.harvard.edu)

Title: The Desirability of Outcome Ranking (DOOR) in Clinical Trials

Bio: Scott Evans, Harvard University is the Director of the Statistical and Data Management Center (SDMC) for the Antibacterial Resistance Leadership Group (ARLG) and a member of the Board of

Directors for the American Statistical Association (ASA) and the Society for Clinical Trials (SCT). Dr. Evans is a recipient of the Mosteller Statistician of the Year Award and is a Fellow of the ASA.

Abstract: Typical benefit:risk assessment in clinical trials is suboptimal due to a failure to incorporate associations between outcomes of interest, competing risk challenges, and since efficacy and safety analyses are conducted on different analysis populations, the population to which these benefit:risk analyses apply, is unclear. We propose the desirability of outcome ranking (DOOR) whereby outcomes are used to analyze patients rather than patients to analyze outcomes, to address these problems and more optimally inform patient treatment.

Contributors

Scott Evans
Marc Buyse
Julien Peron
Dean Follmann
Scott Evans

INVITED SESSION 28 - CLINICAL TRIALS IN CHINA – OPPORTUNITIES AND CHALLENGES
FOR INTERNATIONAL COLLABORATION

YUANYUAN KONG

With the largest population and the fastest growing economy, the number of clinical trials operated in China has increased dramatically in the past 10 years. By the end of 2017, China ranked No.2, second to US only, in the number of interventional trials registered in the www.clinicaltrials.gov. The resources of well-equipped medical institutions, well-trained investigators, and eligible study subjects in China create great opportunities for international collaborations in clinical trials. Meanwhile, there are many unique issues including regulatory management, trial design, data management, and project management. Research hospitals in China tend to design and conduct clinical trials independently from the universities they are affiliated to administratively. Biostatistics, as a graduate training program in Chinese universities, is in its early development stage. Experienced professional trial operation management personnel are highly demanded. The role of study coordinators are often filled by graduate students in medical schools. Secure electronic data capture and clinical trial information management systems remain unavailable to many investigators in academic institutions. Knowing the great opportunities and recognizing the special challenges of running clinical trials in China will pave a wide road toward international collaboration in clinical research and medical innovations.

Dr. Chen Yao is a senior biostatistician from Peking University, serves as the review board member of the China Food and Drug Administration (CFDA). He will discuss the development of statistical guidance and regulatory requirements of CFDA, including regulations, policies, procedures, and guidance for new drug review process.

Dr. Hong You is a physician at the National Clinical Research Center for Digestive Diseases in Beijing Friendship Hospital. She will share her experiences of managing an academic research organization (ARO) in China, both gains and pains. Her presentation will include the infrastructure, management of collaborative research network of clinical trials, regulatory issues on bio-sample management, ethical consideration on patient privacy and interest protection.

Dr. Yuanyuan Kong, a biostatistician from Capital Medical University, will discuss the procedures for project development, study design, trial operation, data collection, and data analyses, based on the clinical research network of Gastrointestinal and hepatobiliary diseases in China. Her presentation will also cover the use of information technologies in clinical trials, such as mobile apps for subject randomization, electronic data capture systems, and data extraction from institutional health information systems, and issues related to protected health information, data sharing, intellectual property protection, and good publication practice.

Dr. Valerie Durkalski-Mauldin, a senior biostatistician and director of the Data Coordination Unit at the Medical University of South Carolina, will present her perspectives on clinical trial collaboration

between US and China with a particular focus on the investigator initiated NIH-funded clinical trial setting

Contributors

Jidong Jia

Chen Yao

Hong You

Yuanyuan Kong

Valerie Durkalski-Mauldin

INVITED SESSION 29 - PLACEBO AND SHAM CONTROLLED TRIALS IN SURGERY AND IN OTHER INVASIVE PROCEDURES: LESSONS, ETHICS AND DESIGN ISSUES

DAVID BEARD

Using a placebo control or comparator is often thought as the “best” trial design to investigate healthcare interventions. A placebo reduces several biases which otherwise undermine a comparative study’s validity. Placebo controlled trials in surgery and other invasive procedures, however, are highly controversial for ethical and design reasons. The construction of a suitable placebo or sham intervention, the achievement of satisfactory participation/acceptance by surgeons and other key personnel (e.g. anaesthetists) and interpretation of the trial can all be challenging. In this session we will present recent advances in the understanding of the design considerations, conduct and ethical arguments surrounding placebo controlled trials in this area. We will discuss the implications for the choice of placebo control (considering development and pilot work) raised by a recent review of placebo-controlled trials in surgery, and the design and conduct issues raised using the conduct of the recently completed placebo surgical trial (the CSAW trial, a placebo surgical controlled trial of sub-acromial decompression for shoulder pain) as a case study. We will also discuss the current ethical arguments for and against the use of sham surgical controls and whether such trials violate clinical equipoise. The role of research ethics committees in the assessment of placebo controlled surgical trials will also be discussed. The session will bring together an international faculty with direct experience of the design, conduct and ethical challenges posed by placebo trials in surgery. The session will involve invited talks each covering different aspects of the use of placebo controls in surgery followed by a moderated discussion of key themes.

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Speakers include:

Professor Marion Campbell, University of Aberdeen, UK – Trialist and methodologist: Prof Campbell will provide an introduction to the concept and role of placebos in surgical trials and review the current international regulatory frameworks influencing their use.

Professor David Beard, University of Oxford, UK – Trialist and Chief Investigator of the placebo-controlled surgical CSAW trial: Prof Beard will discuss the issues raised by, and lessons learned from, the design and conduct of a recent placebo controlled trial in surgery.

Professor Charles Weijer, Western University, Ontario, Canada – Ethicist: Prof Weijer will review ethical arguments for and against the use of sham surgical controls and discuss whether such trials violate clinical equipoise or pose undue risks to patients. He will also assess the roles and responsibilities of research ethics committees in determining whether the social value of the question outweighs risks to patients.

Professor Jane Blazeby, University of Bristol, UK – Academic Surgeon and Trialist: Prof Blazeby will discuss the implications for the choice, development and piloting of surgical placebo controls raised by a review of the literature and recent work being undertaken to classify the separate components of surgical interventions and placebo comparators.

Session discussant:

Professor Jonathan Cook, University of Oxford, UK – Trialist and methodologist: Prof Cook will lead a moderated discussion with the panel and audience around key themes raised by the presentations

Contributors

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Marion Campbell
David Beard
Charles Weijer
Jane Blazeby
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INVITED SESSION 30 - REPRODUCIBLE CLINICAL TRIALS

DENISE ESSERMAN

SPEAKERS TENTATIVE TITLES:

Michael Kane (michael.kane@yale.edu) - Defining Reproducibility in Clinical Trials (Challenges and Opportunities)

Prasad Patil (prpatil42@gmail.com) - Implementing Reproducible Research in Medicine

Denise Esserman (denise.esserman@yale.edu) - Reproducible Clinical Trial Design for Patient Centered Outcomes Research (PCORI)

Tze L Lai (lait@stanford.edu) - Processes for Reproducibility and Case Studies at Stanford's Center for Innovative Study Design

PROPOSED SESSION TYPE:

We propose an invited session with 4 invited talks plus a panel discussion. (15-20 minute talks with a 10-20 minute discussion).

Reproducibility is essential in clinical research. It puts the field on sound scientific footing, it allows other members of the community to interrogate current results, and it facilitates discovery. For example, it is not generally distinguished from replicability (in lay terms). However, there currently isn't consensus on the definition and implementation of reproducibility. Furthermore, we as a community, have not clearly defined reproducibility in the context of clinical trials. This session explores: How to define a reproducible clinical trial; and how to build a framework so that clinical trials are truly reproducible. More specifically, we aim to define reproducible research as it pertains to clinical trials. We will introduce the areas of a clinical trial where we need to be meticulous in documenting our thought process: design, data, analysis. We will discuss examples of ways that this can be done in a systematic fashion. We will make suggestions as to how this can be implemented in a standardized fashion - so that we don't just have reproducible components, but that we can have a reproducible trial - start to finish.

Dr. Michael Kane is an Assistant Professor in the Department of Biostatistics at Yale University. He will give an overview on the data science perspective on reproducible research, defining a reproducible design, data, analysis and trial. Further, he will discuss clinical trial compendiums for scientifically rigorizing trials.

Dr. Prasad Patil is a postdoctoral fellow at the Harvard Chan School of Public Health Department of Biostatistics/Dana-Farber Cancer Institute Department of Biostatistics and Computational Biology. He worked with Drs. Roger Peng and Jeffery Leek at Johns Hopkins to formulate a statistical definition for reproducibility and replicability. He will discuss his work in formulating these definitions and how they pertain to clinical trials.

Dr. Denise Esserman is an Associate Professor in the Department of Biostatistics at Yale University. She will discuss her work in developing a web application and R packages for the reproducible

design of clinical trials. This talk will focus on the design aspect of clinical trials- as often times it is difficult to reproduce the exact sample size used to design a trial.

Dr. Tze Liu is the Ray Lyman Wilbur Professor of Statistics at Stanford University. He has been working with Drs. Phil Lavori and Narasimhan Balasubramanian at Stanford's Center for Innovative Study Design. Dr. Liu will present processes that have been implemented at the Center for providing reproducibility. He will also present several case studies based on clinical trials performed by Stanford clinical researchers.

Contributors

Shing Lee
Michael Kane
Prasad Patil
Denise Esserman
Tze Lai