2018 SCT EDUCATION OFFERINGS – PORTLAND, OR ANNUAL MEETING

HALF-DAY WORKSHOPS – MORNING (8:00 AM – NOON)

Workshop P1
Adaptive Multi-arm Platform Trials

Traditionally, clinical trials have been designed to evaluate a single treatment in a homogeneous group of patients. Such trials have proven useful for answering the following question: "Does a single treatment offer a benefit on average to a study population?" However, the answer to this question does not provide the physician with the necessary information to make decisions regarding the best treatment for an individual patient, especially when the patient may differ from patients in the study population and there are multiple treatment options to consider.

In addition, medical research is quickly moving beyond the simplistic view of an average treatment benefit in a homogenous group of patients. Biomarker development and personalized medicine are leading to a future in which the vast majority of diseases will be rare diseases. This will make slow, large scale clinical trials with a single hypothesis within a single disease impractical to conduct, and the speed of medical discovery will outpace the planned completion of such trials. Advances in personalized medicine are also leading to increasingly complex treatment regimens. This is forcing researchers to address a different question: "Which treatment or combination of treatments is best for each type of patient?" The answer to this question will provide the practicing physician with the information needed to make informed decisions on individual patient care.

To efficiently answer the latter (and more relevant) question, we advocate the use of adaptive multi-arm platform trials. Platform trials have master protocols that evaluate multiple treatments across one or more types of patients. Adaptive platform trials are especially useful for exploring heterogeneity and interactions of treatment effects, evaluating combinations of treatments, and for direct comparisons between competing treatments. The sharing of resources in platform trials, possibly between multiple sponsors, can greatly reduce costs and increase statistical efficiency. Adaptive platform designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial. In an era of personalized medicine, adaptive platform trials provide the innovation needed to efficiently evaluate modern treatments.

This workshop will explore the motivation and principles underlying adaptive platform trials. We will demonstrate that adaptive platform trials can find beneficial treatments with fewer patients, fewer patient failures, less time, and with greater probabilities of success than traditional strategies. We will also provide real examples of innovative adaptive platform trials, demonstrating how simulations are used in the design stage to evaluate operating characteristics and to refine prospective adaptive protocols using simulated example trials. We will discuss challenges (both statistical and logistical) associated with the implementation of platform trials and regulatory interactions.

Outline:

- 8:05-8:50am: Roger Lewis Introduce adaptive platform trials: Motivation, advantages, evolution of medical research & science, etc. Adaptive platform trials from a physician's perspective Discussion of PREPARE CAP: European adaptive platform trial for community acquired pneumonia
- 8:50-9:25am: Hands-on small group activity based on response adaptive randomization
- 9:25-9:45am: Ben Saville Efficiencies of adaptive platform trials relative to traditional designs

- 10:15-11:00: Jason Connor Discussion of GBM-AGILE: A global platform trial for brain cancer
- 11:00-11:45pm: Ben Saville Discussion of an Ebola platform trial design: Preparing for the next Ebola pandemic Highlight other innovative platform trials
- 11:45-12pm: Q&A

Target Audience: Statisticians, clinicians, and researchers involved in clinical trial design

Goals: Educate the clinical trial community on 1) the purpose of a platform trial; 2) the benefits and efficiencies of adaptive platform trials; 3) the process of designing an adaptive platform trial via simulation; and 4) the challenges associated with adaptive platform trials

Requirements: None

Faculty: Ben Saville, Berry Consultants
Roger Lewis, Harbor-UCLA Medical Center
Jason Connor, ConfluenceStat, LLC

Workshop Liaison: Kousick Biswas, VAMHCS, CSPCC

Workshop P2

Design and Conduct of Efficient, Innovative Pilot & Feasibility Studies for Complex Interventions

Efficient, well designed and conducted early phase studies are vital to ensuring robust design and implementation of large scale clinical trials. Pilot and feasibility studies are distinct from phase I/II studies and adaptive designs, and are studies conducted in advance of definitive phase III trials to inform the feasibility and design of the future phase III trial. The CONSORT Statement (BMJ 2016) related to pilot and feasibility studies provides a detailed description: http://www.bmj.com/content/355/bmj.i5239.

This workshop will focus on feasibility and pilot studies, conducted in advance of definitive phase III randomized controlled trials evaluating complex interventions. It will give an overview of key design considerations, relevant literature and discuss practicalities to ensure efficient and smooth conduct. The presenters will use diverse examples from their extensive portfolio of feasibility and pilot studies to illustrate key points and to aid small group discussion, sharing successful solutions to challenges in study conduct.

The workshop will describe the main study designs and definitions, particularly the distinctions between feasibility and pilot studies, and between internal and external pilots and include different considerations relevant to individually and cluster randomized feasibility and pilot studies. It will also include a discussion of the sample size requirements appropriate to individual designs and provide details relating to defining progression criteria. The workshop will discuss practical issues encountered when conducting these types of studies and offer solutions to optimize efficient study implementation. The workshop will highlight examples of best practice, key publications, and discuss reporting standards. Small group work with feedback will enable discussion between participants, and will focus on four topics, with around 30 – 40 minutes devoted to each:

1. Design decisions and specifying research questions;
2. Sample size considerations;
3. Defining progression criteria;
4. Practical considerations for efficient conduct.

The workshop will conclude with a round-up of all group discussions and will summarize key learning points.

Outline:

- Interactive introductory presentation to cover definitions, designs, and key considerations (e.g. feasibility vs. pilot, internal vs. external pilots), key publications, practicalities of conducting these studies with example of best practice and reporting (45 mins);
- Design decisions and specifying the research questions: small group work (20 mins) and feedback (10 mins);
- Sample size considerations: short presentation/overview (10 mins) followed by small group work (20 mins) and feedback (10 mins)
- Defining progression criteria: short presentation/overview (10 mins) followed by small group work (20 mins) and feedback (10 mins)
- Practical considerations for efficient conduct: presentation/overview (15 mins) followed by small group work (15 mins) and feedback (10 mins)
- Final round-up (15 mins)

Target Audience: Clinicians, investigators, trial & data managers, and statisticians with an interest in designing and/or conducting pilot and feasibility studies for complex intervention evaluations.

Goals: By the end of this workshop, attendees will:

1. Understand the design and rationale for various types of pilot and feasibility studies, including specifying appropriate research questions;
2. Understand the key determinants of appropriate sample sizes for these types of studies;
3. Learn how to specify robust progression criteria, relevant to each type of design;
4. Gain knowledge of practical considerations for efficient study implementation.

Requirements: None

Faculty: Amanda Farrin, University of Leeds
Michelle Collinson, University of Leeds

Workshop Liaison: Li Chen, Amgen, Inc.

Workshop P3
Understanding adaptive designs through phase II single-arm trials

Single-arm trials remain the design of choice for many phase II oncology trials. Consequently, it is generally appreciated that it is important, for anyone interested in clinical research, to have knowledge of the available statistical procedures for such trials. An under-appreciated aspect of single-arm trial methodology, however, is that it provides an effective route to understanding the logic behind, and techniques required for, implementing design adaptations in more complex randomized trial settings. With interest in adaptive designs increasing, this makes awareness of innovative statistical techniques for single-arm studies of even more pronounced value.

It is these techniques upon which our course will focus. We will discuss a range of classical and contemporary procedures for adaptively designing, and subsequently analyzing, single-arm trials. Moreover, we pay particular attention to describing how this relates to adaptive trials more generally. And finally, practical sessions will provide participants with the chance to gain experience in using the range of software that is now available for designing and analyzing single-arm trials.

Overall, our course will provide participants with extensive knowledge of single-arm trial methodology, within the context of adaptively designing studies more generally. Those who are interested in learning about these important topics, whether they have previous experience of such techniques or not, will find this course particularly interesting.

Outline:

- Single-arm trial design:
    - 45-min lecture: We will first describe procedures for designing group-sequential single-arm trials (including Simon's two-stage design). A selection of more modern techniques will then be detailed, including adaptive two-stage designs, designs incorporating curtailment, and Bayesian designs.
    - 15-min software presentation: Next, we will demonstrate the use of available software in R and Stata for the design of single-arm trials, including the OneArmPhaseTwoStudy package.
    - 45-min practical: Participants will work through a selection of computer exercises, motivated by real clinical trials, in their choice of R or Stata. This will reinforce various ideas introduced in the preceding lecture; including e.g. how to choose a design that is efficient in a range of possible scenarios.
    - 10-min discussion: A short period of time will be reserved for attendees to ask questions on single-arm, or adaptive, trial design.
- Single-arm trial analysis:
    - 30-min lecture: Following this, we will focus on single-arm trial analysis. We will begin with a lecture on maximum likelihood estimation, and the problems associated with this when analyzing sequential data. Adjusted procedures for specifying point estimates, confidence intervals, and p-values, will then be described; including the UMVUE.
    - 10-min software presentation: A second presentation period will be utilized to explicate the use of software for single-arm trial analysis.
    - 30-min practical: A final computer practical session will see participants explore issues of trial analysis through a selection of worked exercises. Particular attention will be paid to how single-arm trials with binary outcomes provide the opportunity to assess the exact properties of estimation procedures.

    - 10-min discussion: As above, time will then be reserved for participants to ask any questions that they may have on the analysis of single-arm trial data.
- Hypothetical single-arm trial activity:
    - 30-min group work: In this period, a more hands-on approach will be taken to exploring many of the issues that arise in the design and analysis of single-arm trials. Participants will split in to small groups to work through an exercise based on an example trial scenario. Specifically, hand-out led deliberations will proceed on possible factors that could influence appropriate trial design (including, e.g., selecting the number of possible stages).
    - 10-min discussion: We will conclude by reviewing the group discussions from the above activity, and with a final opportunity for attendees to ask any questions they may have.

Target Audience: Anyone interested in learning about single-arm or adaptive design methodology, including but not limited to clinical trial statisticians and methodologists.

Goals: For participants to: a) learn about the most recently developed methodology for the design and analysis of single-arm trials b) learn about the potential advantages of adaptive trial design c) gain extensive experience in using relevant statistical software.

Requirements: Please bring your own laptop with R or STATA installed

Faculty: Michael J. Grayling, MRC Biostatistics Unit
Adrian P. Mander, MRC Biostatistics Unit

Workshop Liaison: Yves D. Rosenberg, NHLBI, NIH

HALF-DAY WORKSHOPS – AFTERNOON (1:00 PM – 5:00 PM)

Workshop P4
Novel Adaptive Designs for Early Phase Clinical Trials

Statisticians and physicians are always looking for more efficient ways to determine the safety and efficacy of new regimens in early phase trials, in order to move to determine which regimens should forward to potential practice-changing phase III trials. This short course will cover a variety of novel designs for phase I and II clinical trials. The objective of phase I trials is to find the maximum tolerated dose and recommended phase 2 dose. The objective of phase II trials is then to investigate the preliminary efficacy of the treatment, and determine whether it is promising enough to test in large phase III confirmative trials. The course will begin with an overview of phase I designs, with particular focus given to clarifying their statistical foundations, differences, and pros and cons. The remainder of the course will cover novel Bayesian phase II designs, including those based on posterior probability and predictive probability. Trial examples and software will be described and demonstrated so that attendees can apply these novel methods to design their own clinical trials in practice.

Outline:

1. Algorithm-based design and its limitation (Alexia 30 min).
2. Model-based designs:
    - Single-agent: Continual reassessment method (CRM) (Alexia 45 min).
    - Multiple-agent: Partial order (PO)-CRM, and others (Nolan 45 min).
3. Model-assisted designs: Modified toxicity probability integral (mTPI), Bayesian optimal interval (BOIN), and keyboard designs (Ying 45 min).
4. Phase II designs based on posterior probability and predictive probability (Ying 30 min).
5. Software for implementing the designs (Nolan and Ying 30 min).

Target Audience: Biostatisticians and clinical trialists with an interest in learning about novel adaptive designs for early phase clinical trials. This short course will be given at an introductory level, and will focus on the basic concepts, and the application of, novel phase I and II designs. Formal statistical training is recommended, but not required.

Goals: For participants to: a) learn about novel phase I dose finding trial designs b) learn about state-of-the-art Bayesian phase II trial designs c) have a hands-on session to learn about software for designing novel early phase trials.

Requirements: Bringing your own laptop is encouraged

Faculty: Ying Yuan, University of Texas MD Anderson Cancer Center
Nolan Wages, University of Virginia
Alexia Iasonos, Memorial Sloan Kettering Cancer Center

Workshop Liaison: Michael Grayling, MRC Biostatistics Unit

Workshop P5

How to use IDEAL (Idea, Development, Exploration, Assessment and Long-term study) to improve surgical innovation and medical device evaluation

Surgical procedures are complex interventions; whose characteristics pose serious challenges to developing high quality randomized controlled trials. As a result, regulators have not required such trials before permitting widespread use, in contrast to pharmaceuticals for which licensing systems require valid RCT evidence of safety and efficacy. Surgical innovations therefore frequently gain acceptance based on evidence from biased observational studies. The relative lack of regulatory pressure, together with the unique characteristics of surgical interventions, has resulted in persistent difficulties in obtaining high-quality evidence for surgical innovations. Assessment of new surgical interventions is complicated by a specific set of problems. These include the difficulty in defining surgical procedures precisely, iterative modification of procedures by surgeons during development, lack of agreed standard outcomes in surgery, operator learning curves, variable procedural quality (dependent on training and operative capabilities), as well as strong treatment preferences among patients and clinicians. Recognition of these difficulties led to the development of the Idea, Development, Exploration, Assessment and Long-term follow-up (IDEAL) Framework and Recommendations, in an attempt to establish a more scientifically rigorous and ethical evaluation pathway. [1, 2] There are many similarities in the challenges of evaluating new medical devices and IDEAL has been applied in this area in the IDEAL-D version of the Framework. [3]

1. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC et al., No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009 Sep 26; 374(9695):1105-12
2. Pennell, C.P., et al., Practical guide to the Idea, Development and Exploration stages of the IDEAL Framework and Recommendations. British Journal of Surgery, 2016. 103(5): p. 607-615
3. Sedrakyan Art, Campbell Bruce, Merino Jose G, Kuntz Richard, Hirst Allison, McCulloch Peter et al. IDEAL-D: a rational framework for evaluating and regulating the use of medical devices BMJ 2016; 353 :i2372

Outline:

- 60 minute section: Two presenters
    - Explore the inherent challenges of surgical research and how to deal with them
    - Introduction to IDEAL and IDEAL-D - why and how it arose and what it is. Framework of stages and practical recommendations for research answering key research question at each stage.
- 45 minute section: Two presenters
    - Small group-work in groups of 5-6 people. Use tools developed by IDEAL to identify which IDEAL Stage techniques have reached by reviewing the existing literature. Facilitated group feedback and discussion.
- 60 minute section: 1 presenter
    - Applying IDEAL – Small group work in new groups of 5-6 people. Groups will be given an innovation idea and asked to consider issues and practicalities of how to deal with each IDEAL stage to progress the technique/device through the life-cycle of surgical innovation. Groups will feedback with facilitated discussion.
- 30 minute section: 1 presenter
    - Current status and future of IDEAL. Interactive session where participants will work in pairs to consider how they and other stakeholders can use IDEAL in research, healthcare

coverage decisions, HTA and regulation. A to-do list for future work for IDEAL will be created.

- 30 minutes: Plenary Questions / reflections – All

Target Audience: Surgeons, non-clinical research professionals and industry representatives involved in planning, conducting and publishing surgical or device related evaluation studies. Trainees from all disciplines wishing to understand more about surgical research methods will find this session helpful.

Goals:

- Understand the particular challenges of conducting surgical and device research
- Understand the purpose of IDEAL and why it is necessary
- Understand the stages of the IDEAL Framework and relevant questions at each stage
- Learn how to identify the IDEAL stage of a research study and appraise surgical papers using tools developed by IDEAL
- Learn how to apply the IDEAL framework and recommendations to designing studies appropriate to the life-cycle stage of a surgical innovation or device

Requirements: Brining your own laptop is encouraged.

Faculty: Allison Hirst, University of Oxford
Asha Khachane, Maimonides Medical Center
Joel Horovitz, Maimonides Medical Center
Joshua Feinberg, Maimonides Medical Center
Peter McCulloch, University of Oxford

Workshop Liaison: Lynda Constable, University of Aberdeen

Workshop P6

A tutorial on sample size for efficient cluster, cluster cross-over and stepped-wedge randomized trials; and introduction to an online "app"

Determining required sample sizes for cluster randomized trials involves a complex interplay between practical and cost or logistical constraints, and the desire to achieve a statistically efficient trial design. One commonly used approach is to simply determine the power or detectable difference for the available number of clusters and available average cluster size. However, given the importance of maximizing the social and ethical value of trials, it is essential to consider the trade-offs between designs with a larger number of smaller clusters and a smaller number of larger clusters. The methodological literature has seen substantial development in sample size calculation approaches for longitudinal designs, such as cluster cross-over, parallel arm with repeated before and after measurements, and stepped-wedge designs. When these designs are feasible, they can substantially increase the statistical efficiency of the trial. However, there are multiple methodological complexities that need to be considered before adopting these designs. For example, correlation structures become more complex as they may depend not only on the cluster but also the time separation between repeated measurements, and whether the repeated measurements are made on the same or different participants.

In this tutorial we will summarize the current methodological literature on sample size calculation for cluster randomized trials, with special attention to longitudinal designs including the cluster cross-over and the stepped-wedge. Participants will be introduced to different ways of accounting for correlations in longitudinal cluster trials – an essential feature of any sample size calculation. We will also describe different ways of estimating these correlations empirically, so that they can inform calculations in the real world. We will then introduce and illustrate software including a web-based "app" which will allow researchers to implement these procedures in a straightforward way. The software will also allow researchers to more clearly appreciate the conventional trade-offs between cluster size and number of clusters, as well as the relative statistical efficiencies of different longitudinal designs.

The sessions will have a substantive interactive element to allow attendees (whether statisticians, health professionals, trialists, or other researchers) to apply the methods. Case studies and examples from clinical trials will be used to illustrate the techniques. Participants will spend time in small groups working through some illustrative case studies on their own, and applying techniques learnt.

Outline:

- Keynote address (15 minutes): A brief history of the development of cluster randomized designs from the simple parallel to the stepped-wedge. Speaker: Professor Jim Hughes
- Part 1 (45 minutes): Overview of sample size calculation procedures for simple and longitudinal cluster randomized trials. Speaker: Monica Taljaard
- Part 2 (30 minutes talk + 30 minutes group work): Introduction to a web-based "app" for designing longitudinal cluster randomized trials and methods for estimating key correlation parameters. Speaker: Karla Hemming
- Part 3 (30 minutes talk+ 30 minutes group work): Extending the correlation structures of longitudinal cluster trials to non-uniform correlation structures with illustration using freely available software. Speakers: Andrew Forbes and Jess Kasza
- Part 4 (30 minutes talk + 30 minutes group work): Designing longitudinal cluster trials to detect treatment heterogeneity with introduction to implementation software. Speaker: Jim Hughes

Target Audience: Our target audience is researchers and statisticians who are involved in the design of cluster randomized trials; but who wouldn't consider themselves experts in the area. The session will be accessible to researchers who are not statisticians as our intention is to allow all researchers involved in the design of these trials to understand the importance of efficient study design. A beta-version of the on-line application is available at: https://clusterrcts.shinyapps.io/rshinyapp/.

Goals:

1. To summarize current sample size methodology for longitudinal cluster randomized trials (including conventional parallel arm and stepped-wedge design);
2. To introduce participants to different ways of conceptualizing within cluster correlations in longitudinal cluster trials; and present ways of estimating these key parameters for the purpose of sample size calculations;
3. To illustrate software including a web-based "app" which will allow researchers to implement sample size calculations for these studies in a straightforward way.

Requirements: Bringing your own laptop is encouraged

Faculty: Karla Hemming, University of Birmingham, UK
Monica Taljaard, Ottawa Hospital Research Institute, Canada
Jess Kasza, Monash University, Australia
Andrew Forbes, Monash University, Australia
Jim Hughes, University of Washington, USA

Workshop Liaison: Jody Ciolino, Northwestern University

EVENING WORKSHOPS (7:00 PM – 9:00 PM)

Workshop P7
Adaptive Designs: How Can We Achieve the Promise?

In recent years, there has been substantial interest in the use of adaptive clinical trial designs that provide the flexibility to allow for design modifications during an ongoing trial. Unfortunately rapid proliferation of research on adaptive designs, large number of proposed adaptations, and inconsistent use of terminology has created confusion about the similarities, and more importantly, the differences among the techniques. Furthermore, the implementation of adaptive designs to date does not seem consistent with the increasing attention provided to these designs in the statistical literature. Focus on some specific barriers that impede the use of adaptive designs in the current research environment. The workshop will conclude with an open discussion focused on future efforts that are needed in order to ensure that clinical trialists achieve the promised benefits of adaptive designs.

The structure of the workshop will primarily be didactic, incorporating many examples of adaptive designs that the presenter has been involved with. However, due to the almost infinite possibilities for adaptation in clinical trials, it is recognized that the audience likely has a very heterogeneous experience with the use or past interest in these types of design. Thus, the last 15-20 minutes of the workshop will be allocated to an open discussion about how some of the issues discussed in this workshop may apply to projects the workshop participants are or have been involved with.

Target Audience: This workshop is intended for a general clinical trials audience. The discussion will not be technical in nature, and requires no background in statistics. Rather, the discussion will primarily be operational – providing a better understanding of what is considered a proper adaptive design, current challenges associated with the use of adaptive designs, and consideration of ways to address these challenges in the future.

Goals: For participants to gain a better understanding about the similarities and distinctions among various types of adaptive designs, as well as the logistical and regulatory barriers associated with the use of these designs. To accomplish this, the workshop has three objectives:

1. Clarify some of the confusion surrounding the use of these methods
2. Focus on some specific barriers that impede the use of adaptive designs in the current research environment
3. Summarize the results of a few recently completed surveys to assess the interest and attitudes of the clinical trials community in general with respect to adaptive designs

Requirements: None

Faculty: Christopher S. Coffey, University of Iowa

Workshop Liaison: Emily Dressler, Wake Forest Baptist Health

Workshop P8
Studying Treatment Mechanisms – A Whistle Stop Tour of Simple Mediation Analysis

Clinical trials have large resource requirements, and we should make the best use of these resources to maximize information gained about treatments under study. Trials usually aim to answer the question "Does the treatment work?", but they can also answer the question "How does the treatment work?" In other words, in addition to estimating treatment effects, our trials can provide information about treatment mechanisms using mediation analysis. Mediation analysis is used widely in psychology and psychiatry, but is potentially underused in other fields. By using it to study mechanisms, we can learn how treatments are working and potentially how they could work better. Mediation analysis aims to determine whether treatments are having the expected effects on their physiological targets, and in turn whether these physiological effects have the expected knock-on effect on outcomes. This provides researchers with an evidence base to support informed refinement of treatments, increasing the likelihood of improved patient outcomes.

This workshop will give participants a chance to gain an understanding of what research questions mediation might be able to address in their field, as well as improve their ability to critically appraise published mediation analyses. Participants will be given the opportunity to provide possible mediation scenarios, and the presenter, who is an expert in mediation analysis, will lead a group discussion. The presenter may also provide additional examples where mediation can answer interesting research questions. Finally, participants will perform a simple mediation analysis in a software program of their choice (Stata, SAS or SPSS).

Outline:

- What is mediation? An introduction (30 minutes)
    - The concept of mediation will be introduced, including: how it allows the study of treatment mechanisms, what needs to be done in a trial in order to pose and answer mediation questions, and the structure of a simple mediation model.
- Ask The Expert interactive activity (30 minutes)
    - Participants will be asked to send examples ahead of time via email of scenarios where they think mediation analysis might answer a question of interest, and these will be discussed as a group. The presenter may also prepare some potential mediation scenarios from a range of fields that she will bring along and circulate (via slides and/or handouts) in order to stimulate a discussion.
- How do I run a mediation analysis? Small group hands-on software practical (45 minutes)
    - Participants will be provided with some example data and software code for running a simple mediation model and have time to practice performing and interpreting a simple mediation analysis in small groups with support from the presenter/organizer. The organizer plans to present examples using the Stata, SAS and SPSS software programs, with participants asked to provide their preferred statistical program ahead of time.
- Open discussion and wrap-up (15 minutes)

Target Audience: Researchers/statisticians who want to study mechanism/mediation analysis as part of their clinical trials. These may be individuals who want an introduction to mediation analysis in order to assess its utility in their field (including a software introduction), or who want to start using mediation analysis and want support in getting started with such analyses.

Goals: For participants to: a) understand the purpose of a mediation analysis/the questions such an analysis can answer, b) provide some potential examples of mediation analysis in their field for discussion during an "Ask the Expert" session, c) understand a simple mediation analysis and how to write/run software code to produce such an analysis in Stata, SAS or SPSS.

Requirements: Laptop installed with an appropriate version of the chosen software installed and any add-ons or specific commands downloaded (the latter information will be provided to participants beforehand); A good understanding of regression modelling and basic proficiency in the delegate's chosen software program (either Stata, SAS or SPSS)

Faculty: Kimberley Goldsmith, King's College London
Graeme MacLennan, University of Aberdeen

Workshop Liaison: Lynda Constable, University of Aberdeen

Workshop P9
Training the Next Generation of DMC Members and the Teams that Support Them

Data Monitoring Committees (DMCs) are an important component of the clinical trial process. They are charged with reviewing interim data and making recommendations to protect the safety of trial participants and ensure the scientific integrity of the study. This tutorial will cover beginning, intermediate, and advanced topics regarding the DMC process and how all participants in the DMC process – the DMC members, the sponsor team and the Statistical Data Analysis Center (SDAC) supporting the DMC - can better work together. The goal is for attendees to learn more about their own role and the roles of the other two groups.

The session will focus on best practices as enumerated by regulatory guidance and the recent CTTI white paper, as well as from the presenter's 20 years of experience working on DMCs and attending 500 DMC meetings. There will be time for questions-and-answers from the audience throughout the presentation, especially in regards to specific issues the audience has faced in the past.

Specific topics to be discussed will include the history of DMCs and current guidance documents; the organizational flow of the DMC process and the responsibilities of those involved; DMC meeting structure, timing, and purpose; logistics of DMC membership including assessment of conflict of interest; DMC review of study conduct, safety, efficacy (possibly with formal boundaries); closed session interaction between the SDAC and DMC; hallmarks of a good SDAC; DMC recommendations including considerations for recommending premature termination of the study or alternatives; and examples of "tricky situations" sometimes faced by the DMC and the SDAC and how to deal with them.

Outline:

- 'DMC 101' – 20 minutes presenting and 5 minutes of Q&A – focusing on the basic organizational flow of the DMC process and the key responsibilities of the three core groups.
- 'DMC 102' – 30 minutes presenting and 5 minutes of Q&A - focusing on interactions between the three core groups and the DMC meeting structure and the type of outputs the DMC receives.
- 'DMC 103' – 25 minutes presenting and 5 minutes of Q&A – focusing on the DMC decision making that takes place during the Closed Session and considerations the DMC should take into account to make the most appropriate recommendations.
- 'The Final Exam' – 30 minutes of open-ended questions posed to the audience for the audience to discuss, with input provided by the presenter.

Target Audience: Anyone interested in the Data Monitoring Committee (DMC) process – 1) current or potential DMC members, 2) statisticians, medical monitors, project managers and data management personnel on the study team that are working with DMCs, and 3) independent statisticians from Statistical Data Analysis Centers (SDACs) supporting DMCs

Goals: The goal is to train DMC members, study team members from the sponsor, and independent statisticians from the SDAC on the current best practices of the DMC process and provide illuminating anecdotes so that future DMCs can be even more effective in protecting patient safety and ensuring the scientific integrity of the study.

Maximum Enrollment: Room Capacity

Faculty: David Kerr, Axio Research
Kent Koprowicz , Axio Research

Workshop Liaison: Kevin Buhr, University of Wisconsin - Madison

IN-CONFERENCE TUTORIALS (90 minutes each)

Workshop IC1
StatTag for Connecting R, SAS, and Stata to Word: A Practical Approach to Reproducibility

Reproducibility, wherein data analysis and documentation is sufficient so that results can be recomputed or verified, is an increasingly important component of statistical practice and publication of scientific studies. Clinical trials in particular have been subject to increased scrutiny and requirements for data sharing. To address this challenge, we have created StatTag, a free, open-source program that embeds statistical results from R, SAS, or Stata directly in Microsoft Word.

StatTag is available as a Word plugin (Windows) or standalone application (Mac) that links statistical code files to Word documents. From Word, users attach one or more code files to an active document, and use the StatTag interface to "tag" selected statistical output - estimates, tables, or figures. The user instructs StatTag to insert the selected statistical output into the Word document, and StatTag invokes the appropriate statistical software and places the result within the document text. Inserted results can be updated automatically or on demand, and double-clicking a result provides the exact code used to generate it. The StatTag interface also allows direct user interaction with the code file; users may view, edit and re-run statistical code directly from Word.

StatTag is well suited for clinical trials, where ongoing monitoring and reporting are necessary, and updating results manually represents a substantial burden of time. For example, consider a CONSORT flow diagram for a Data Safety Monitoring report regularly updated over an enrollment period of months or years.

While generating updates of the requisite numbers for the diagram is a simple task with any statistical programming software, preparing the diagram for inclusion in a Word or Excel document, would either require advanced programming knowledge to fully generate the figure within the statistical software system or else would involve a time-consuming manual process of copying updated results to an existing Word or Excel figure, compromising reproducibility and potentially introducing errors. By using StatTag, an analyst, investigator, or coordinator who can construct a CONSORT flow diagram directly within Word or Excel can also populate the diagram with results using StatTag, updating the diagram automatically whenever enrollment changes without the effort and potential risk of human transcription errors.

Outline:

- Introduce approaches for reproducible research with focus on data analysis and publication (10 minutes)
- Introduce StatTag, a reproducible research tool for Word with SAS, Stata and/or R (15 minutes)
- Lead a hands-on session during which participants will generate an abstract with StatTag in the software version of their choice (60 minutes)
- Connect users to the StatTag knowledge base and summarize the information learned (5 minutes)

Target Audience: This course is intended for a broad audience; prerequisites are experience preparing documents in Word and conducting analysis in any one of R, SAS, or Stata. The workshop will provide practical, hands-on examples drawn from R, SAS, and Stata, and will include an overview of approaches to reproducible research as well as an introduction to StatTag. This course will be of interest to all individuals who participate in data management, analysis, and publication of clinical trials.

Goals: (1) Introduce participants to StatTag and other reproducible research software. (2) Teach participants to use StatTag, leaving with a completed abstract using the statistical software of their choice. (3) Connect participants to the StatTag knowledge base and resources for using StatTag in their own research.

Requirements: A laptop operating either Microsoft Windows 7 or higher or macOS 10.11 or higher. Laptops have Microsoft Word (Windows: Word 2010 or higher; macOS: Word 2016) and a supported statistical software package (SAS: v9.4 or higher, Stata: v14 or higher or R: v3.0 or higher). Participants will need administrative privileges to install software. Participants should download and install StatTag (www.stattag.org) prior to the beginning of the tutorial.

Faculty: Abigail Baldridge, Northwestern University
Leah Welty, Northwestern University

Workshop Liaison: Stacey Slone, University of Kentucky

Workshop IC2
Engaging 'tricky' sites: hints and tips

Effective site management is critical to the successful and timely completion of multi-center clinical trials. Most trial managers have experience with sites where start-up is delayed, recruitment slow, compliance with the intervention poor, and/or loss to follow-up high. Much time is spent trying to resolve trial site difficulties, sometimes at the expense of overall trial progress.

This workshop will present information on possible solutions for managing these 'tricky' sites. We will present practical examples, facilitate small-group assessment of a series of case studies/scenarios, and encourage participants to discuss issues with expert facilitators and share ideas with each other.

Our international workshop faculty members have experience in coordinating national and international publicly funded and industry trials, as well as recruiting patients and managing activities at clinical centers. The small group work will be supported by expert facilitators from both the UK and North America, all of whom have worked in a variety of settings and will bring their varied experiences to this workshop.

Outline:

- Introduction (Alison 2 min)
- Strategies to enable effective interaction with trial sites and study partners (Carol Knott, 20 mins).
- Small group work. We will divide participants into small groups of around 6-8 people. Based on a mixture of common and less familiar problems encountered during trial set-up and when study is 'live', each group will be asked to identify and describe methods to manage sites to maximize trial performances. (Group work, 40 mins).
- Feedback from each group – A representative of each group will give feedback on the group's discussions and other groups will be invited to comment (All, 25 mins).
- Summary and conclusion (Heidi approx. 3 mins).

Target Audience: Project Managers, Trial Managers, Clinical Research Associates, anyone else interested in improving the quality and efficacy of the clinical trial sites in their studies.

Goals: For participants to: a) learn methods and look at suggested tools for managing 'difficult' trial sites, b) share experience and best practice with colleagues to increase effectiveness of sites c) participate in a hands-on session learning to identify 'red-flags' and how to work with under-performing sites to improve performance, in particular recruitment and retention.

Requirements: None

Faculty: Carol Knott, University of Oxford
Alison McDonald, University of Aberdeen
Heidi Krause-Steinrauf, George Washington University

Workshop Liaison: Jessica Wood, University of Aberdeen

Workshop | IC3
Statistical Graphs in SAS Using Graphics Template Language (GTL)

Historically, users of SAS who are tasked with creating statistical graphs for analyses and manuscripts have had either PROC GPLOT or PROC SGPLOT as their only real options. In recent releases of SAS, a new option is available, Graphics Template Language (GTL). GTL can be used to create a large array of highly customizable statistical graphs. GTL can create, both single graphs and panel graphs, and the process of annotating graphs with additional information – often tedious in GPLOT – is straightforward in GTL. All GTL graphs can be easily incorporated into PowerPoint presentations, and since they are generated in vector-based formats, they are suitable for submission to medical journals requiring such formats.

However, GTL is not typical SAS syntax and can be intimidating at first glance. This session is designed to reduce the intimidation factor by breaking down FTL syntax into its component parts. We will present aspects of GTL syntax and concepts and provide several live, hands-on exercises.

The session will begin with a background of what GTL is and how it makes a graph. A brief exercise will follow which will show users how to view the underlying GTL templates that SAS uses to produce ODS graphics associated with any given procedure's output. We will then turn to LIFETEST's hidden output dataset, which SAS uses to generate a standard survival graph. This dataset, which is very versatile, is not documented in SAS User's Guides. A second exercise will explore how changes to the LIFETEST procedure call impacts the contents of this dataset. Finally, we will provide a detailed description of how to make a GTL template from scratch for a survival plot, followed by a hands-on exercise where participants will add additional information to the graph. This exercise will include:

- Making the SAS dataset for the graph
- Employing dynamic variables so that data not included in that dataset (e.g., a p-value) can be added to the graph
- Modifying the template to incorporate that additional data
- Generating the actual graph file

There will be time at the end for any questions.

Target Audience: Attendees who are tasked with creating statistical graphs using SAS who want a flexible and powerful alternative to GPLOT/SGPLOT.

Goals: After the presentation, attendees should have: - a) Become familiar with the concept of layouts in GTL, b) Learned how to pair different layouts in order to produce a complex graph, and c) Learned how to incorporate data from multiple procedures in one graph

Requirements: Laptop with SAS installed

Faculty: Rebecca Paulus, American College of Radiology

Workshop Liaison: Kathryn Winter, American College of Radiology

Workshop IC4
Using Studies within a Trial (SWATs) to increase the evidence base for trial recruitment and retention decision-making

Randomized trials are at the heart of clinical guidelines affecting the care of millions of people around the world and are central to evidence-based health care systems. It is odd then that the evidence available to trial teams to inform their own decisions about trial design, conduct and dissemination is so sparse. This is true for many trial processes from choice of research question through dissemination of results but this workshop will focus on two processes: recruitment and retention.

At least half of trials fail to recruit to target, and those that succeed often fail to retain participants, with half of trials losing more than 10% of their participants before the primary outcome is measured. While more than 25,000 trials a year are reported, the evidence base to support evidence-informed recruitment and retention strategies is remarkably thin, despite the fact that both processes are critical to trial success.

This interactive workshop will present the current state-of-the-art in the science of recruitment and retention and also introduce a key tool in the methods evaluation armory- the Study within a Trial (SWAT). We will explain the need for coordinated and collaborative work so that trustworthy evidence can be generated within years instead of decades. We will consider the opportunities, challenges, barriers and enablers for routine evaluation of recruitment and retention interventions in ongoing trials. We will also discuss interventions that are widely used but have little or no evidence of benefit to support their use. We will provide a funder perspective.

This workshop will give participants a chance to expand their knowledge regarding trial recruitment and retention, understand the importance of coordination and collaboration in making meaningful improvements in the evidence base, and explore their own ideas regarding priorities for methodology research in recruitment and retention. Participants will collaborate in an evaluation of a SWAT design developed by them during the workshop.

Outline:

- Introduction (Shaun, 3 mins)
- The state-of-the-art of research on trial recruitment (Shaun Treweek, 8 mins).
- The state-of-the-art of research on trial retention (Katie Gillies, 8 mins).
- A tool to increase the evidence base: the Study within a Trial (SWAT). A funder's view. (Andrew Cook, 8 mins).
- How running SWATs could help trials in North America and elsewhere (Jeremy Grimshaw, 8 mins).
- Small group work. We will divide participants into small groups of around 6-8 people. Based on known gaps in the evidence coming from presentations 1 and 2, each group will be asked to select a gap and design the outline of a single recruitment or retention SWAT that could help to fill that gap (Group work, 30 mins).
- Feedback from each group – A representative of each group will give feedback on the group's discussions and other groups will be invited to comment (10 mins).
- Open discussion and summing up (approx. 15 mins).

Target Audience: Anyone interested in improving the evidence base for trial recruitment and retention.

Goals: For participants to: a) learn the current state-of-the-art in recruitment and retention b) learn about SWATs as a way of increasing the evidence for recruitment and retention decisions c) have a hands-on session to develop a SWAT that can go on to collaborative evaluation.

Maximum Enrollment: 50

Faculty:	Shaun Treweek, University of Aberdeen Katie Gillies, University of Aberdeen Jeremy Grimshaw, University of Ottawa Andrew Cook, National Institute of Health Research Spencer Hey, Harvard University
Workshop Liaison:	Emily Dressler, Wake Forest Baptist Health

Workshop IC5

PRECIS-2: Precisely how can this tool help investigators design trials to achieve practical answers to "real world" questions?

Designing clinical trials is challenging and there is a risk that trial design decisions such as the choice of outcome or comparator could render the trial irrelevant to its intended users. "The PRECIS-2 tool: Designing trials that are fit for purpose" was published in the BMJ 2015 and describes a tool to help clinical trial designers think more carefully about the impact their design decisions have on the applicability of the trial results. PRECIS-2 is being used by the National Institute of Health (USA) to assess proposed trial designs and is recommended by the Irish Review Board to support grant applications. The PRECIS-2 tool was developed and validated with the input of over 80 international trialists, clinicians, and policymakers.

This interactive workshop will introduce the key design domains that need to be considered to ensure that a trial is relevant to the intended users of its results. We will then describe how the tool can facilitate decision-making and conversations among investigators and other stakeholders. Small group work will give workshops participants the opportunity to obtain hands-on experience applying the tool to a trial. Current projects using the PRECIS-2 tool will be used to illustrate different applications of PRECIS-2 and highlight how it can be applied to a wide range of trials. Facilitators will lead an interactive discussion of how workshop participants might use the tool in their own trial design work, including how to handle cluster designs and trials with multiple arms. The possible uses of the tool in future pragmatic and comparative effectiveness trial research will also be discussed.

This workshop will give participants a chance to expand their understanding of the different design considerations for pragmatic and explanatory trials and the consequences of design decisions on applicability of results. Participants will also explore how the tool may be applied prospectively in designing trials.

Outline:

- Introduction to the PRECIS-2 tool and the domains (Kirsty) – (8mins)
- Group Exercise
    - Introductory example. Brief explanation of what we are doing (4 mins)
    - Materials: Handouts with PRECIS-2 information sheet for everyone (BMJ table with all domains) plus information on our example trial.
    - Small group work: We will divide participants into small groups of around 6-8 people. Each group will be asked to prioritize 3 PRECIS-2 domains (e.g. Eligibility, and Recruitment and Setting) for the trial example (25 - 28 mins).
    - Feedback from each group – A representative of each group will provide feedback on how the group scored each domain: what they used to reach this score, difficulties they had, things they would like to discuss, strengths and weaknesses of the tool. Other groups will be invited to comment (20 mins)
- Two presentations (15 mins in total)
    - Paula Darby Lipman (Westat) working with PIs for NIH funded pragmatic trials (USA)
    - Andrew Cook (NIHR) on how tool can be useful from a funder's perspective (UK)
- Open discussion (15 mins) on the PRECIS-2 tool to close the workshop
    - Questions from participants on the last two presentations
    - Discuss participants' experience and ideas for use of tool
    - Final comments from the workshop facilitators

Target Audience: Anyone interested in ensuring that trial design decisions match the needs of those who are expected to use trial results decision making.

Goals: For participants to a) learn about PRECIS-2 b) learn how it is being used in the US and the UK by funders c) have a hands-on session of using the tool d) have the opportunity to discuss the tool, its uses and challenges with the designers of the tool, other participants and users.

Maximum Enrollment: Room Capacity

Faculty: Kirsty Loudon, University of Stirling, UK
Paula Darby Lipman, WESTAT, Rockville, USA
Andrew Cook, National Institute for Health Research, UK
Shaun Treweek, University of Aberdeen, UK
Heidi Gardner, University of Aberdeen, UK
Adel El Feky, University of Aberdeen, UK

Workshop Liaison: Joy Black, University of Michigan