Programme of Abstracts

2017 PSI Conference

Grange Tower Bridge Hotel, London

14 - 17 May 2017

CELEBRATING 40 YEARS OF PROMOTING STATISTICAL INSIGHT

Welcome Letter

On behalf of the PSI Conference Organising Committee, I'd like to welcome you to London and The Grange Tower Bridge Hotel for the 40th Annual PSI Conference. To signify this major milestone, this year's theme will be Celebrating 40 years of Promoting Statistical Insight.

We are delighted to welcome our two keynote speakers who will be opening the conference on Monday and Tuesday morning. On Monday, Richard Stephens will be sharing with us a patient's perspective on the changes he has seen over the last 40 years in patient participation in drug development. On Tuesday, David Spiegelhalter, Winton Professor for the Public Understanding of Risk, Professor of Biostatistics and Fellow of Churchill College at Cambridge University will present on Engaging without Manipulating: the Balanced Communication of Statistics.

This year's conference saw a record number of contributed abstracts submitted for both oral and poster presentation. We are also introducing a new one minute highlight session for the Posters on Monday afternoon. Over the three days we can now look forward to four plenary sessions, 21 parallel sessions, including two workshops, with a total of more than 60 speakers.

The conference App proved to be a huge success last year so it is available for download again this year and will keep you up to date with all the latest information, session plan, speaker abstracts and biographies, as well as all the social events taking place, including this year's James Bond themed Gala Dinner "The PSI who Loved me".

I would like to invite you to take advantage of all of the opportunities this conference brings with it; in meeting with old colleagues and friends, making new associates, learning something new and above all having fun! The conference is a huge undertaking, taking ~18 months to come together and I couldn't do it without the constant support of a fantastic committee.

The Scientific Committee currently comprises 19 statisticians (to see who, go to the Committee page on the App) working at various companies across the pharmaceutical industry and throughout Europe who work hard all year, on a voluntary basis, to put together an agenda that will be relevant and interesting to such a wide audience. I hope you all agree that the programme looks fantastic and, like me, you will find it difficult to choose between the sessions. Thank you to everyone who has been involved in the organisation of the conference!

I would also like to take the opportunity to thank all of our exhibitors and sponsors as we would be unable to run this event without your continuing support.

> **"This year's conference saw a record number of contributed abstracts submitted for both oral and poster presentation."**

As usual, after the conference we will be contacting you with a link to the electronic feedback form. Your feedback is very important to us in planning future conferences and we especially welcome ideas for future topics you are interested in or ways to further improve the conference to make it a better experience for you. You can also provide feedback to me or anyone else in the committee throughout the conference, we are always happy to hear your thoughts.

I look forward to meeting as many of you as I can this year, and wish you all an enjoyable and successful 40th conference.

Lucy Rowell, Roche Products Ltd
Conference Chair

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Monday 15 May:

Opening Remarks

Mark Morris, PSI Chair, will welcome you to London and formally open the 2017 PSI Conference.

40 years of PSI - From Patients Staying Ignorant, Through Patients Showing Interest, to Patients Starting Involvement

Our keynote Richard Stephens, editor-in-chief of BioMed Central's Journal of Research Involvement and Engagement will open the conference.

Background: The past 40 years have brought huge changes in the UK's health relationships. Whilst much political and managerial discussion has been spent on formal contractual relationships of commissioners and providers, and on structures, funding and performance, the impact of social change has also taken effect. Concepts such as "patient choice" and the need to provide timely and accurate information to patients to support that choice, are recognised and embedded in constitutions and charters, if not yet delivered across all diseases and all locations. Meanwhile the wider implications of "consumerism" and "active citizenship" are bringing the benefits and challenges of Patient Involvement into the clinical research world, and especially into clinical research delivered in the NHS.

Method: This presentation is based on the personal views on the author's journey through healthcare over the past 40 years. From learning at the breakfast table with mum, a nurse trained in the war, through sports injuries and a first diagnosis of cancer in 1998, to more diagnoses, more time as a patient, and active involvement as a patient advocate in health research since 2002.

Discussion: The presentation will explore issues raised by the author's experience of cancer treatments and cancer research. It will cover his own time as a carer and as a patient, including his participation in 4 clinical trials and 9 observational studies. However it will focus on his learning from 14 years of Patient Involvement in research, with NCRI and NIHR, RfPB and HTA, UCL and MRC, with Pharma and biotechs, charities and universities, with Eupati and patient organisations and health trusts in the UK devolved nations, with studies, programmes and national bodies, in prevention, diagnosis and treatments, and above all, his views as the Patient Member of the Independent Cancer Taskforce, one of the authors of the current national Cancer Strategy, and one of the prime exponents that the patient experience is as important as the clinical outcomes.

Method: I grew up being told that patients should not argue with Doctors ... Now I am telling individual patients to research their own illnesses and put evidence in front of their doctors, and I tell patient groups that we should play an active and equal part on obtaining the evidence in the first place, including working with industry. In another 40 years active citizens will be looking to make contributions to research every time they are ill; the NHS will not distinguish between treatments, research and evidence-gathering, and the life sciences industry and academia will each be an integral part of our country's economy and our way of life and social fabric too. If, that is, we make the right changes and choices now.

Estimands:

The way we think about clinical trial design, conduct and analysis is likely to undergo a step-change thanks to the much anticipated release of the draft ICH E9 addendum on estimands. Prior to the release of the guidance document, expected in mid-2017, this session will discuss where we currently stand and postulate on possible future directions.

The regulatory views of Robert Hemmings (MHRA, CHMP member and rapporteur of the ICH E9 addendum working group) will be complemented by those of Lisa LaVange (Director of the Office of Biostatistics, CDER at FDA). The industry perspective will be provided by Chrissie Fletcher (Amgen and member of the ICH E9 working group). Importantly, this topic is not only statistical. It is a multi-disciplinary effort that requires a common understanding and buy-in beyond the statistics community. The session would thus not be complete without the clinical perspective on the framework and the upcoming addendum, which will be given by Wolfgang Kothny (Medical Director at Novartis).

Speakers:

1. Rob Hemmings (MHRA)
2. Chrissie Fletcher (Amgen)
3. Lisa LaVange (FDA)
4. Wolfgang Kothny (Novartis)

Decision Making in Drug Development

Speakers:

1. Nelson Kinnersley (Roche Products Ltd): "From molecule to medicine: a case study in how a statistician can provide strategic input to drug development"

When evolving the design of a clinical trial, statisticians may spend a considerable amount of time to optimise certain characteristics of the proposed trial and there is considerable literature to support such work. However, the literature is more sparse on the strategic factors that a statistician should consider

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when involved with designing an entire drug development programme. The aim of this work is to use a suitably anonymised case study to inform the practising statistician about the considerations for strategic drug development.

Through liberal use of scenarios covering topics such as Target Product Profile (TPP), Clinical Development Plans (CDP), gating criteria and probability of success we will offer suggestions for how a statistician can contribute to strategic drug development. Many concepts are applicable across a variety of therapeutic areas even if the technical implementations may differ. It is hoped that with a wider understanding of strategic drug development, more statisticians can be better equipped to contribute to the cross-functional teams who perform this type of work when the plans are being developed for how to turn a molecule into a medicine.

2. Gaelle Saint-Hilary (Dipartimento di Scienze Matematiche (DISMA), Politecnico di Torino): "Comparing drug development strategies with probabilities of success including benefit-risk assessment to inform decision-making"

Evidence-based quantitative methodologies have been proposed to inform decision-making in drug development, such as metrics to make go/no-go decisions, predictions of success based on the statistical significance of future clinical trials or benefit-risk ratios. While these methodologies appropriately address some critical questions on the potential of a drug, they either focus only on efficacy or consider the past evidence without predicting the outcome of the future trials, failing to account for the multifaceted aspects of a successful drug development. We propose a more comprehensive approach using a composite definition of success for a development strategy, based not only on the statistical significance of the treatment effect on the primary endpoint, but also on its clinical relevance, and on a favourable benefit-risk balance versus the comparator(s) in the next pivotal studies. For one drug, we compare several development strategies before starting the pivotal trials by comparing their predictive probability of success. The predictions are based on the available evidence from the previous trials, which could be combined with new hypotheses on the future development. The resulting predictive probability of composite success provides a useful summary to support the discussions of the decision-makers. It has been efficiently used in an actual decision problem, which we have illustrated using a fictive, but realistic, example in Major Depressive Disorder.

3. Simon Kirby (Pfizer): "Selection bias for compounds with positive Phase 2 results"

Only compounds with positive Phase 2 results are chosen for further development. This selection based on positive results produces a bias. In this presentation, we look at how this bias can vary according to study design and the criteria used to declare a trial positive. We also consider analysis methods which adjust results for this bias. The topic is important when Phase 2 results are projected forward to predict the results of Phase 3 trials and to estimate the probability of success of the Phase 3 trials.

Pharmaceutical Statistics: Our Journal Over The Years

David Morgan will introduce this session as the Pharmaceutical Editor in Chief

Speakers:

1. Simon Day (CTCT): "(Still?) Changing Times in Pharmaceutical Statistics"

In the first two issues of the journal, way back in 2002, I reflected on recent changes I had observed in the pharmaceutical industry and speculated on some aspects of what might happen next (at least up until around 2020). Some of my speculations were intentionally provocative but, still, some of them have come true (e.g. anyone considered going to prison as a result of their involvement on a data monitoring committee!?) Some of my speculations have not materialised but these are, without doubt, merely censored observations waiting to happen.

I will reflect on what I got right and what I got right but hasn't yet happened, but more importantly on current changes and, in some cases, lack of changes. Openness of data and all round greater transparency must surely be one of our biggest changes – and we haven't yet seen the bulk of it. Brexit, of course, will be so important to our industry that it won't even need mentioning.

2. Kevin Carroll (KJC Statistics): "Oncology is not so different (as many claim it to be)"

Over the past decade, progression-free survival in oncology has increased in prominence and importance in oncology drug development, particularly in licensing decisions where PFS and related measures have, in an increasing number of situations, surpassed overall survival as the basis for approval. With the profile of PFS increasing, issues relating to how such data are handled and analysed have been the focus of a lot of statistical research. While the basic fundamentals highlighted in "PFS, some common statistical issues" (2007) and "active-controlled, non-inferiority trials in oncology" (2006) are as applicable today as they were 10 years ago, much has moved forward in the intervening period, including work on interval censored approaches, new guidance and publications on NI trial design, publications on the value of centralised review of progression outcomes and an increasing focus on 'crossover' analyses in oncology. I will reflect on some of these developments, both good and not so good, and what, if putting pen to paper today, I might have said differently.

3. Andy Grieve (UCB): "Type I / Type II Error Control in Drug Development"

The traditional method of designing clinical trials in drug development is to the type I error at a fixed small value and to choose the sample size to control the type II error or power. Implicit behind this approach is the assumption that a type I error is more critical than a type II error. Is that always true? Absolute control of the family-wise type I error is a mantra drummed in to young statisticians, which lead Stephen Senn

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to quip that 95% of PhD theses in German speaking Europe had to do with controlling the type I error at 5%. Is that what should be our target? Another approach is to design a decision rule based on clinical reasoning an investigate the operating characteristics of the rule under a range of null and alternative scenarios and accept that perfect calibration is not a requirement. In this talk I review two papers I published in recent issues of Pharmaceutical Statistics which investigate these ideas.

References:

Grieve AP. How to test hypotheses if you must. Pharmaceutical Statistics 2015; 14:139-150.

Grieve AP. Idle thoughts of a 'well-calibrated' Bayesian in clinical drug development. Pharmaceutical Statistics 2016; 15:96-108.

Biosimilar Development

Speakers:

1. Johanna Mielke (Novartis) "Introduction to biosimilarity assessment"

The development of biosimilars has recently has gained much attention A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine which is called the reference medicine. Although the idea of biosimilars is not unlike the concept of generic drugs, biosimilars are not comparable to generics because their molecules are much larger and they are manufactured in living cells, which makes it impossible to produce an exact copy of the original product. These fundamental differences also lead to differences in the development cycle and approval process. This talk gives an introduction into biosimilar development and highlights some of the statistical challenges.

2. Heike Woehling (Sandoz): "Case study and practical considerations"

Sandoz biosimilar studies intend to address all aspects of biosimilar development to fulfil the requirements for worldwide submissions. In this presentation a case study will be presented using a novel clinical trial design to demonstrate similarity in efficacy, safety and immunogenicity between a biosimilar and its reference drug. This design not only follows the principles from the FDA and EMA biosimilar guidelines, but also accounts for switching aspects between the two drugs. Due to the fact that the relevant biosimilar guidelines are not aligned in all aspects, several partly contradicting design and practical features have to be taken into considerations. These aspects will be presented and discussed in respect to the case study.

3. Franz König (Medical University of Vienna): "Regulatory aspects and review of EMA authorized biosimilars"

In 2006, Omnitrope (by Sandoz) was the first approved biosimilar in Europe. In 2016 21 biosimilars for seven different biologics were on the market. In this presentation we summarize the findings of a comprehensive review of all clinical trials of authorised biosimilars using the European public assessment reports (EPAR) published by the European Medicines Agency (EMA). The compared features were, among others, number of patients involved, number of trials, study designs, endpoints and equivalence margins of pharmacokinetic (PK)/pharmacodynamics (PD) and phase III trials. We found that the variability between the clinical development strategies is high. Some differences are explainable by the characteristics of the product: if, for example, the PD-marker can be assumed to predict the clinical outcome, no efficacy trials might be necessary. But even for products with the same reference product, the sample size, the endpoints and the statistical models are not always the same. There are also approved biosimilars where not all primary endpoints met the equivalence criteria. In the last part we will discuss clinical trial designs, where a successful trial is defined when only k out m comparisons yield equivalence and how samples sizes are affected by using different success-criteria. In summary, there seems to be flexibility for sponsors regarding the decision as how to best prove biosimilarity.

Richard Nixon: Lifetime Achievement

Speakers:

1. Valda Murphy (Novartis): "Richard Nixon, achieving significance through the application of statistical methods to life"

I will talk about my experience of Richard's passion for statistics and propensity for applying statistical models to a wide variety of life situations.

2. Oliver Sander (Novartis): "Richard Nixon at Novartis"

This talk will share my view of Richard's work in the pharmaceutical industry at Novartis (in particular in decision analysis and structured benefit-risk) and some of the personal takeaways of working with him.

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3. Deborah Ashby (Imperial College London): "Better benefit-risk decision-making in the regulation of medicine"

Until recently, assessment of the benefit risk balance for a medicine has been entirely informal, but there is now growing interest among drug regulators and pharmaceutical companies in the possibilities of more formal approaches to benefit-risk decision-making. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was a project funded under the Innovative Medicines Initiative as a collaboration between academic, pharmaceutical, regulatory and patient organizations. Richard Nixon was a pivotal member of the team, bringing both academic rigor and a deep understanding of the pharmaceutical context. Based on work from PROTECT we review current methodological approaches, and illustrate them with the case-study led by Richard on nataluzimab for multiple sclerosis where benefit-risk is finely balanced. We will introduce the PROTECT Benefit-Risk Roadmap, designed to help those wishing to find their way through this evolving arena.

4. Simon Thompson (Cambridge University): "Richard Nixon at the MRC Biostatistics Unit, Cambridge (2000-2007): Nasty bivariate distributions for cost-effectiveness analyses"

Young Statistics Methodology

Speakers:

1. Erik Doffagne (CluePoints S.A., Mont-Saint-Guibert): "Detecting atypical correlations in multicenter clinical trial data"

In this paper, we focus on the detection of an atypical correlation between two numeric features, such as the height and weight or the systolic and diastolic blood pressures in multicenter clinical trials. Our work finds its primary motivation in the field of statistical monitoring and the detection of data fabrication in clinical trials. It extends to any application where the correlation between two numeric features should be compared across various data collection centers.

Data from multicenter clinical trials are complex. Center-effects are generally observed resulting from the natural differences in the patients enrolled in the centers or from other systematic differences between centers. The statistical comparison of the correlation observed in one center and the correlation observed in all other centers should not rely on simplistic models that neglect these effects. We present an algorithm based on a random effects model that performs a robust statistical comparison between the correlation observed and expected in any given center. As a result of the algorithm, a P-value is returned for each center that reflects how atypical the observed correlation is in the center. The performance of the algorithm is discussed and results are illustrated on data from several studies.

2. Lorin Miller (GCE Solutions): "ODMAD Algorithm for Mixed Attribute Outlier Detection"

Statisticians traditionally utilize distance based outlier detection techniques such as Grubbs Test or Cook's Distance, but these methods only support continuous variables with distributional assumptions and dimensionality restrictions. However, we know that there are often categorical variables that provide additional information on what constitutes as an "outlandish" value. For example, the typical height for a female is different than that of a male. It also might be useful to find if a dataset contains any unusual categorical values in the possible event of a typo in the dataset. While there exist some techniques that resolve these issues, many of them require predictive nature through regression which does not always provide an appropriate solution. The ODMAD algorithm addresses all of these concerns by implementing a two phase process. It first checks for infrequent categorical values and any infrequent combinations of values, and then it searches for numeric outliers by applying either more traditional detection approaches, or cosine similarity for high dimensional numeric data, on all subsets of categorical values. ODMAD combines simple, yet effective methodologies with the traditional numeric approaches that all statisticians know, making it both easy to implement and flexible across an array of dataset types.

3. Anastasiia Raievska (Veramed Ltd): "Prognostic accuracy of pulmonary function tests, in Idiopathic Pulmonary Fibrosis (IPF), to select patients at high risk of Acute Exacerbations: A Retrospective Case-Control Study"

Idiopathic Pulmonary Fibrosis (IPF) is a rare, progressive disease that causes scaring of the lungs, which is often fatal. Forced Vital Capacity (FVC) is a conventional regulatory clinical endpoint which measures how much air a person can exhale during a forced breath. Trials with FVC as a primary endpoint require long follow up and large sample sizes. Consequently, an alternative endpoint needs to be used for Proof of Concept studies. The time to Acute Exacerbation (AE-IPF), Hospitalisation or Death may be used instead if the population can be enriched with patients who are likely to experience one of those events. All these outcomes are correlated and patients who experience AE-IPF have a higher probability of hospitalisation and death. To check whether the study can be enriched with patients who are likely to have AE-IPF we analysed data from retrospective observational case-control study in patients with IPF who experienced AE-IPF, and matched IPF controls who did not experience AE-IPF. Three pulmonary function tests (%FVC, %FEV1 and %TLCO) as well as the Composite Physiologic Index (CPI) were compared in terms of their prognostic capabilities of an AE-IPF event using univariate and multivariate analyses, a GLM model with repeated measures and Cox-PH-regression with time-varying covariates. ROC curves were used to define cut-offs for CPI and combination of other 3 PFT parameters to identify patients with high risk of AE-IPF. Models with CPI showed good discriminative power to detect patients at high risk of AE-IPF.

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Tuesday 16 May 2017

Engaging without Manipulating: the Balanced Communication of Statistics

Opening the second day of the conference is David Spiegelhalter, Winton Professor for the Public Understanding of Risk, Professor of Biostatistics and Fellow of Churchill College at Cambridge University.

Numbers are often deliberately presented in a way that makes them either look big, say to alarm us, or small, perhaps to reassure us. They are essentially used as rhetorical devices to influence our emotions, as any time spent listening to the radio will reveal. The challenge is to engage interest in the stats without influencing opinion in a particular direction, and I shall discuss attempts being made to do this in health and other disciplines.

Integrated Data Analysis

Speakers:

1. Andrew Bate (Pfizer): "Lessons from meta-analyses of Randomized Clinical Trials for Analysis of Distributed Networks of Observational Databases"

Networks of constellations of longitudinal observational databases, often Electronic Medical Records or Transactional Insurance Claims or both, are increasingly being used for studying the effects of medicinal products in real world use. Increasingly such databases are configured as distributed networks with patient level data are kept behind firewalls. Data are standardized across the network, and queries of the network are executed locally by data partners, and summary results provided to a central research partner(s) for amalgamation, aggregation and summarization. Such networks can be huge covering years of data on upwards of 100 million patients, an example being the FDA Sentinel Network. There are some similarities in this new emerging field with the field of Randomized Clinical Trials (RCT) meta-analysis. Similarities and differences are reviewed and suggestions for how on how learnings from meta-analysis research may help guide the development of distributed network analyses of longitudinal observational databases are provided.

2. Sally Hollis (University of Manchester): "A unified framework for synthesis of safety data in the presence of varying exposure and risk"

There is increasing focus on the value of the availability and use of individual participant data (IPD) as opposed to study-level data for meta-analysis. The integration of safety data is often challenging due to varying duration of exposure across studies. When utilizing IPD, a key opportunity is the ability to examine both trends in risks over time windows of clinical relevance and the impact of short and long term exposure. This can be achieved by using grouped survival analysis methods that enable the incorporation of changes in risks and risk ratios over time intervals. We will present a meta-analysis model, developed by a workgroup within the EFSPI Integrated Data Analysis SIG, which allows the combination of short and long term exposure within a single integrated exposure framework. The key is to introduce information on the individual length of exposure in the assessment of safety risks. This approach proposes a departure from the use of "short-"and "long-term" data pools which re-use data from the same trials when inspecting effects in different exposure intervals. The method allows for changing risk ratios and adjusts for different risk backgrounds which could vary over time. A motivating example of a Rheumatoid Arthritis development program will be introduced. Through simulation, we will assess how well various methods can detect signals within such a program, and examine the potential impact of differential drop-out.

3. Sally Lettis (GSK): "Reporting Adverse Drug Reactions in Product Labels: Suggestions for Improvement"

Product labels are intended to provide health care professionals with clear and concise prescribing information that will enhance the safe and effective use of drug products. In this talk I will offer some suggestions on how the reporting of adverse event information in labels could be improved. The inclusion of comparator incidence in product labels will be advocated as a recommended good practice, as it gives health care providers and patients appropriate information to put the absolute risks in perspective. However, crude pooling of data across multiple studies to provide incidences for adverse drug reactions has the potential to give misleading results. It can result in an overall baseline risk that is different among treatment groups due to differing randomization allocations within a study and different baseline risks across studies. An alternative approach based on adjusted incidence proportions will be presented. The talk will use examples to illustrate these points.

Quantifying Effect Sizes

Speakers:

1. Joanne Rothwell (Sheffield University)
2. Jonathan Cooke (Oxford University)
3. Steven Julious (Sheffield University)
4. William Sones (Oxford University)

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Background: Central to the validity of a RCT is a calculation of the number of participants required (the sample size) which provides reassurance that the trial will be informative. Conventionally, this is usually based upon a difference in the primary outcome (target difference) between groups that is desired to be detectable; the corresponding number of participants needed to be recruited is then calculated.

From both a scientific and ethical standpoint, selecting an appropriate target difference is very important. However, it has been neglected until relatively recently. A variety of approaches have been proposed and addressed by a large recent review. However, there is need for greater guidance to aid researchers and funders.

The DELTA2 study was commissioned by two UK academic trial funders (MRC and NIHR) to improve guidance in this area. However, the project has engaged stakeholders from all sectors and the recommendations applicable to all clinical trials whether they be academic or industry sponsored.

This session will present findings from this project and related work as part of a process of engagement with stakeholders prior to finalising the guidance on specifying the target difference in a randomised trial sample size calculation.

Session content:

1. The session will begin with Steven Julious giving a brief introduction to the session and the topic area along with background to the project.
2. This will be followed by the findings from a review by Joanne Rothwell of the sample size calculations of RCTs funded by one of the leading funders in the UK (HTA programme).
3. A summary of the findings from the DELTA2 project will be given by William Sones, including the completed components of the engagement with stakeholders. This will comprise of findings from a Delphi study and also two expert consensus workshops, held to outline the shape of the new guidance.
4. Jonathan Cook will present the new draft guidance regarding the specification of the target difference and related sample size issues will be presented.
5. Finally, Steven Julious will review the session, along with guidance regarding reporting the specification of the target difference, and open the session to PSI attendees for discussion.

A substantive interactive element is intended and PSI session attendees will be encouraged express their views on the draft guidance and what is needed in this area to further improve the guidance.

The intention is for the talks to be followed by interactive discussion with attendees. We would envisage each talk to be 10-15 minutes, allowing sufficient time at the end of discussion.

Cancer Immunotherapy

Speakers:

1. Andrew Lloyd (Phastar): "Statistical Considerations for Safety Assessment in Cancer Immunotherapy Trials"

Cancer immunotherapy products can possess unique characteristics that call into question the utility of traditional oncology drug development paradigms. Kaplan-Meier curves for overall survival for some of these agents show delayed separation of the curves and a plateau at the end. Delayed but prolonged tumor response may also occur and these factors influence statistical considerations for trial design, timing of interim analyses, and assessment of alternative efficacy endpoints. This talk will focus on statistical challenges in the design, conduct and analysis of immunotherapy trials in assessing the safety profiles of these agents compared to cytotoxic and pathway-specific

agents. The immune-mediated adverse events (imAEs) likely related to immunotherapy are inflammatory in nature and exclude AE's with alternative causes. Special considerations are discussed regarding data capture, toxicity management algorithms, and how the toxicity management may affect efficacy outcomes, and trial reporting. Specific recommendations will be made using case studies from approved immunotherapy's.

2. Markus Elze (F. Hoffmann-La Roche AG): "An evaluation of intermediate endpoints for gating of early phase studies with some applications in cancer immunotherapy"

There is renewed interest by sponsors and regulators to use intermediate endpoints (IME) for early phase development. A gating decision for further development frequently has to be made based on limited patient numbers and follow-up time, making the use of OS as primary endpoint unfeasible in most cases. IMEs that mature early and are suitable for the drug's mechanism of action can be helpful to gate the next phases of development. This issue is particularly relevant for cancer immunotherapies, due to late separation of survival curves, challenges in using classic proxies such as PFS to predict ultimate OS benefit, and the need to consider the possibility of tumour pseudoprogression.

Data on responder status and initial lesion shrinkage are available early, while data on lesion change dynamics and progression take longer to mature. Combinations of several endpoints can also be considered, either as a composite endpoints or using dual endpoint gating. In this study, we provide an overview of several established and novel IME, such as objective response rate, duration of response, time in response, durable response rate, and depth of response. We discuss their relative merits and shortcomings. By simulating early phase trials using data from larger late phase trials (including cancer immunotherapies), we investigate the association of IMEs with OS and the robustness of decisions made based on IMEs. We discuss maturity of the IMEs and availability of historical controls.

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3. Marc Buyse (IDDI): "Generalized pairwise comparisons to test cancer immunotherapies"

Generalized pairwise comparisons extend the Mann-Whitney form of Wilcoxon's test, or Gehan's generalization of this test for two samples of (possibly censored) observations. The test uses all pairwise comparisons between two patients, one in the treatment arm and one in the control arm, in terms of one or several prioritized outcomes. Each pair favours treatment, control, or neither. The treatment benefit is the difference between the proportion of pairs in favour of treatment less the proportion of pairs in favour of control; this statistic is called the "net chance of a better outcome". For a single variable, this measure of treatment benefit has a simple relationship with traditional measures of benefit such as the risk difference (for binary outcomes), the mean difference (for continuous outcomes), or the hazard ratio (for right-censored outcomes). The pairwise comparison approach easily incorporates a threshold of clinical relevance in the analysis, making it useful for situations of non-proportional hazards. In particular, when treatments are expected to have a delayed effect, a threshold of m months can be defined to estimate the net chance of a longer survival by at least m months. The test for such a delayed effect has higher power than the traditional logrank test, and is arguably more clinically relevant. Generalized pairwise comparisons also allow several prioritized outcomes to be studied simultaneously, for instance overall survival, time to tumour progression, serious toxicities, symptoms, or quality of life. The versatility of the method makes it attractive to test cancer immunotherapies.

PSI Annual General Meeting

All PSI members are entitled to attend and speak at the Annual General Meeting (AGM).

Advances in Early Phase Trials

Speakers:

1. Chris Harbron (Roche): "Decision Making in the Face of Biomarker Uncertainty"

Background: Increasingly drugs are developed using a biomarker to define a sub-population of increased clinical benefit. However, frequently the prior evidence of the necessity of the marker isn't overwhelming or the exact definition of the biomarker cannot be specified in advance either in terms of a cut-off and/or the optimal assay or biomarker property that will define the sub-population. In these cases studies will typically be run in unselected populations, with analyses performed in both the whole study population and biomarker defined sub-populations. Although many separate biomarker hypotheses are tested, we wish to maintain an overall type-1 error rate.

Methods: With a single biomarker investigated at multiple cut-offs so all populations are nested, the Spiessens-Dubois method controls the overall type-1 error rate by considering the correlation between tests. We generalise this to non-nested tests representing multiple biomarkers which may be correlated but not ordered, still using the intrinsic correlation from overlapping populations to construct an efficient test. This generates sets of significance boundaries all maintaining an overall type-1 error rate which can be optimized according to a variety of different optimality criteria based upon different characteristics of the study including functions of power, effect size and significance levels.

Results: We present and compare using different optimality to optimise the significance boundaries of a study and link this to properties of the biomarkers being investigated. We give guidance as to how this approach may be practically implemented and the beneficial discussions within clinical teams that this will facilitate.

2. Graeme Archer (GSK): "Bayesian Multivariate Approaches to the Design and Analysis of Experimental Medicine Clinical Trials"

Experimental Medicine (EM) clinical trials typically feature a relatively small number of patients and, because the objective of EM is to learn about the biological mechanisms of disease and their interaction with pharmacotherapy, a relatively large number of endpoints. EM trials then, even more than classical clinical trials, require careful thinking about their design and interpretation, to avoid the pit fall of post hoc reasoning. Power statements and Null hypothesis significance testing are of low utility; we need techniques to assess the fitness of many competing mechanistic models. The Bayesian paradigm is a natural framework for this multivariate set-up; we demonstrate how to use multivariate Bayesian methods to design EM studies (and to estimate their probability of success), to assess the utility of the evidence from such studies, and to support Go/No-Go decision-making based on EM study read-outs.

3. Mark Whitlock (Pfizer): "Is high placebo response in clinical studies really a problem?"

The content of this talk challenges the often-stated assumption that an increasing placebo response is a major issue in clinical trials and the cause of a trend for smaller treatment effects observed in clinical trials for major depressive disorder (MDD) in recent years. We re-analyse the 122 MDD trials between 1983 and 2010 that were summarised in the Undurraga and Baldessarini 2012 paper. Re-analysis of this database shows the active and placebo responses to be highly correlated, to the degree that would be expected assuming placebo additivity, and that previous analyses of the relationship between treatment effect

and placebo response have used inappropriate statistical techniques that ignore the inherent correlation caused by the random variability in the observed response. We show that despite the placebo response in MDD trials increasing up to ~1998 there is no evidence this caused a reduction in the estimated treatment effects. Our conclusion is that when random variability in both the active and placebo response is considered, the data show that increases in placebo response have been associated with equivalent increases in the active response supporting the assumption of placebo additivity. The implication of this is that attempts to reduce the placebo response (e.g. through designs such as placebo lead-in or SPCD) are unlikely to increase the treatment effect since they are likely to reduce drug non-specific effects in the treatment arm by a similar amount.

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Improving Influence and Increasing Impact

Speakers:

1. Andy Grieve (UCB)
2. Gemma Hodgson (Qi Statistics Ltd)
3. Margaret Jones (UCB)

The landscape is changing across the pharma industry and as statisticians, in order to continually add value, we must make sure we adapt. This session will focus on what this means for statisticians outside the technical aspects of their role. Of critical importance is self-awareness during our interactions, working effectively in teams, influencing, being customer focussed and understanding our own consulting and leadership styles.

Now more than ever we need to be creative and influential thinkers with business acumen who can work with our colleagues from other disciplines, not just be technical experts - we need to be proactive partners with strong communication skills

This session will highlight to participants, what this means when working as a strategic partner or as part of a larger team. It will include short exercises to illustrate the skills and behaviours discussed and is aimed at statisticians who want to start improving their consultancy style interactions within their internal project teams and other customers and understand the impact of behaviours and interaction preferences.

What is Happening in HTAs

Speakers:

1. Claire Watkins (Clarostat Consulting Ltd): "Adjusting effects for treatment switching in HTA - why, when, which and how?"

Several statistical methods are available to adjust overall survival estimates for the impact of treatment switching. The situations in which such an adjustment may (or may not) be appropriate will be discussed, in particular why this is often performed for health technology assessment (HTA) but not regulatory submissions. The most common methods will be briefly described. Guidance will be provided on how to select which methods are best suited to a particular study, based on the available data and ways to assess whether the underlying assumptions are reasonable.

2. Chrissie Fletcher (Amgen): "IMI GetReal - using real world evidence in R&D and healthcare decision making"

The IMI GetReal project focused on new methods for real world evidence (RWE) generation and RWE synthesis and explored how RWE could be adopted earlier in pharmaceutical R&D and healthcare decision making processes. This involved companies, regulatory agencies, HTA agencies, academics and other stakeholders to work together to generate consensus on best practices in the use of RWE in regulatory and reimbursement decision-making.

GetReal has developed a range of tools, techniques and training materials so the full potential of RWE can be realized including:

1. The RWE navigator for assessing the acceptability and usefulness of Real World Evidence (RWE), and approaches to the analyses of RWE, in estimating the effectiveness of new medicines.

2. Assessing the scientific validity of RWE study designs and analytical approaches, to better inform pharmaceutical R&D and healthcare decision makers on their potential for use in assessment of effectiveness.

3. Identifying the operational challenges of performing RWE studies early in the medicine development process and developing practical solutions to better inform their planning and delivery.

4. Identifying best practice in evidence synthesis and predictive modelling using different types of data to estimate effectiveness of medicines.

The key recommendations and deliverables from GetReal, which finished in March 2017, will be shared and links will be provided showing how to access the materials generated from the GetReal project.

3. Nancy Devlin (Office of Health Economics): "The role of patient reported outcome (PRO) data in HTA: issues in measuring and valuing health"

There is increasing recognition that patient-reported health can provide an important complement to clinical data in understanding the effectiveness and cost effectiveness of health care technologies. However, there are both conceptual and analytical challenges in using PRO data. In this presentation, I highlight some of these, using the example of the widely used EQ-5D, the most widely used 'generic' PRO. In particular, I will address:

- Conceptually, what do PROs measure?
- Analysing patients' self-reported descriptive data.
- Patients' overall assessment of their own health
- Weighting/scoring and 'values': the source of values and implications for statistical inference
- Differences between PRO instruments eg EQ-5D-3L and EQ-5D-5L; what are the implications for HTA?

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Integrating Historical Control

Speakers:

1. Heinz Schmidli (Novartis): "Bayesian synthesis of historical information for robust prediction and extrapolation"

Prediction and extrapolation based on historical information can make drug development more efficient. Two examples are the use of historical placebo data in a new trial, and the use of adult data in a pediatric trial. In the first case, the prediction of the placebo effect based on historical trials allows us to reduce the number of patients randomized to placebo in the new trial. This decreases costs and trial duration, facilitates recruitment, and may be more ethical. In the second case, extrapolation of treatment effects seen in historical adult trials to a pediatric population, allows us to recruit fewer children, with ethical and feasibility advantages. The possibility that the historical information may not be relevant can be taken into account for both prediction and extrapolation.

2. Franz König (Medical Uni. Vienna): ""Threshold-crossing": A Useful Way to Establish the Counterfactual in Clinical Trials?"

A central question in the assessment of benefit/harm of new treatments is: how does the average outcome on the new treatment (the factual) compare to the average outcome had patients received no treatment or a different treatment known to be effective (the counterfactual)? Randomized controlled trials (RCTs) are the standard for comparing the factual with the counterfactual. Recent developments necessitate and enable a new way of determining the counterfactual for some new medicines. For select situations, we propose a new framework for evidence generation, which we call "threshold-crossing." This framework leverages the wealth of information that is becoming available from completed RCTs and from real world data sources. Relying on formalized procedures, information gleaned from these data is used to estimate the counterfactual, enabling efficacy assessment of new drugs. We propose future (research) activities to enable "threshold-crossing" for carefully selected products and indications in which RCTs are not feasible.

3. Andrew Thomson (EMA): "Regulatory Considerations for integrating historical data"

In this talk I will consider some methodological challenges in integrating historical data with clinical trial data. The motivating focus is the recently published Reflection Paper on extrapolation. I will focus on two key regulatory challenges: understanding the Type I error rate of any approach, and how to deal with trial data that is not commensurate with the historical data.

Within a Bayesian framework this is often referred to as Prior-Data conflict, but the challenge is independent of the framework for analysis, and affects frequentist thinking and interpretation as well. The issues of borrowing data for one arm of a trial, as well as two, will be addressed, and a simple frequentist approach to handle this will be discussed and compared to more formal integrated Bayesian analysis.

Interactive and Animated Visualisations of Data

Speakers:

1. Alexander Schacht (Chair) (Eli Lilly)
2. Shafi Chowdhury (Shafi Consultancy)
3. Zachary Skirvanek (Eli Lilly)
4. Simon Cleall (Biogen)

"Interactive and animated visualisations of data - a 21st century approach on understanding and communicating data"

Visualization of data is not a new idea – even though there is a lot of emphasize on it with new software becoming available. They have always been an important complement to summary as a way to effectively tell the story of the results. Traditional visualizations, like line graphs and bar charts, were favoured because they were required to be printable to be included in CSRs & publications. Until recently the focus has been on improving the presentation and legibility of these static plots.

As technology has advanced and the desire for the reader to interact with visualizations has increased these restrictions are increasingly questioned. In the 21st century expectations have shifted to dynamic and interactive solutions. In this integrated session we will examine visualizations of the change of a variable over time in a clinical trial using real example cases. We will first motivate the example of a dynamic visualization followed by a step by step explanation how to develop an animation. Details of interpolating data necessary for the animation will be provided.

Interactivity with the data is especially important for exploring complex data sets in an efficient way. Examples will be provided to show how time and money can be saved by using interactive visualizations rather than large number of tables. Finally we will show how interactivity and animation can be combined. This combination leads to a very positive customer experience both for company internal discussions as well as for external presentation of the data.

These interactive and dynamic visualizations have many advantages. Although they require higher initial investment they save time and money through their usability. Even more importantly, they meet today's expectations on interacting with data & lead to greater transparency regarding the data that, in turn, builds more trusting relationships between companies and other stake holders such as physicians and payers.

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Wednesday 17 May 2017

Innovative Approaches to Trial Design & Methodology

Speakers:

1. Niccolo Bassani (Quanticate): "Assessing Clinical Equivalence in the Early Treatment Time-Points in Rheumatoid Arthritis"

In rheumatoid arthritis (RA), response to treatment is commonly assessed using the American College of Rheumatology Arthritis composite responder score for a 20% improvement (ACR20). Within biosimilars development, the proportion of ACR20 responders is evaluated at a specific time-point, and the difference between treatment groups is compared to a pre-specified equivalence margin using a confidence interval approach.

Recently, however, it's been pointed out that demonstrating clinical equivalence during the earlier time-points, where the rise of treatment effect is usually seen, would provide additional information on biosimilarity because of the greater sensitivity to treatment differences compared to the plateau phase (Kay et al., Ann Rheum Dis 2013).At PSI 2016 conference a poster was presented where data were simulated according to Reeve et al. exponential time-response model (Ther Innov Regul Sci 2013), and different methods for assessing equivalence across time-points were introduced as an alternative to a '2-norm' approach (Choe et al., Ann Rheum Dis 2015), and their performance in terms of power was evaluated under different model parameter settings. In this talk the simulation settings are expanded to also include random effects and missing data under different mechanisms, and Generalised Linear Mixed Models (GLMM) are also evaluated as an alternative method to equivalence assessment in addition to the weighted mean and the Generalised Estimating Equations (GEE) method presented last year. A suggestion on which method is best suited in different scenarios is made based on power considerations, and general conclusions on equivalence assessment in RA are drawn.

2. Dan Lythgoe (Phastar): "Accounting for overdispersed count data – what could possibly go wrong?"

In asthma and chronic obstructive pulmonary disease (COPD) clinical trials the total number or rate of severe exacerbations is typically an important outcome. The Negative Binomial (NB) regression model is appropriate for modelling such data since, as well as incorporating observed patient follow-up times using an offset, it can explicitly account for 'overdispersion' i.e. where we observe more variation in our count data than we would expect if our event counts were drawn from a simple Poisson model. The estimated 'dispersion' parameter is critical to estimating the variance of the treatment effect, and therefore it is extremely important that overdispersion is carefully considered when estimating sample sizes, both at the study planning stage and during the trial using blinded data (Friede and Schmidli 2010, Scheider et al. 2013). Motivated by a recent COPD study we demonstrate how non-constant event rates and incorrectly specified NB regression models can influence the dispersion parameter and mislead the sample size (re-) estimation process. We describe a number of strategies for investigating the behaviour of the dispersion parameter over time and under different model specifications. Moreover we discuss the usefulness of a lesser known heterogenerous NB regression model (Yee 2015) for which the dispersion parameter is permitted to vary as a linear function of covariates.

References:

Friede and Schmidli (2010) Blinded sample size re-estimation with Negative Binomial counts in superiority and non-inferiority trials. Methods Inf Med 2010; 49: 618–624

Schneider, Schmidli and Friede (2013) Blinded sample size re-estimation for recurrent event data with time trends. Statist. Med. 2013, 32 5448–5457

Yee (2015) Vector generalized linear and additive models with an implementation in R. Springer, New York, ISSN 0172-7397.

3. Madhusmita Panda (Cytel): "Measuring Intergroup Agreement And Disagreement"

This work is motivated by the need to assess the degree of agreement between two independent groups of raters. In literature, there are several measures of agreement. Cohen's kappa (Cohen, 1960) is a popular measure of agreement between two raters with values on a categorical scale. Fleiss' kappa (Fleiss, 1981) for categorical scale and Krippendorff's alpha (Krippendorff, 2004) for continuous scale are suitable measures to evaluate agreement within a group of raters. A generalization is needed to measure agreement between two groups of raters. In the literature there are two measures available to deal with this problem. Van Hoeij (van Hoeij et al., 2004) considered consensus method in which ratings of a subject by raters in a group are replaced by one (most common) rating thus reducing the problem to a two rater's problem. Other method proposed by Vanbelle (Vanbelle et al., 2009) is a generalization of Cohen kappa measure for qualitative data. We propose two new methods to measure agreement between two groups of raters for qualitative as well as quantitative data. First is an agreement measure which is the cube root of product of agreement values within each group and in the combined group of raters. Second is the disagreement measure which is a quadratic form of difference vectors. Properties of two measures are investigated by resampling approach. The two new measures proposed seem to have smaller variability than measures available in literature.

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Combination Trials Across Therapeutic Areas

Speakers:

1. Pavel Mozgunov (Lancaster University): "Randomized dose escalation design for drugs combination cancer trials with immunotherapy"

"For decades, in oncology, the paradigm for dose-finding trials was the more the better as the chemotherapeutic agents had greater activity but greater toxicity as dose increases. Recently, immunotherapy has been shown to have a strong anti-tumor activity and many novel combination treatments investigate either the added value of immune checkpoint blockers to standard therapy or the added value of a new agent to an immune checkpoint blockers. In both situations, one agent is administered at fixed dose. Due to a specific of immunotherapy action, in addition to the detection of the maximum tolerated combination (MTC) the question of testing the clinically significant difference (CSD) of toxicity probabilities on the MTC and standard therapy arises. Although the randomization is not used in early-phase oncology trials and one-parameter models are favoured, we advocate that both goals could be achieved only though the randomization between the escalation and standard arms together with flexible combination-toxicity model. While a one-parameter model almost always declares CSD regardless the underlying scenario, the randomization incorporated with 4-parameter logistic model increases the probability of correctly found CSD by nearly 10% on average comparing with 2-parameter logistic model. Due to less patients on escalation arm, the randomization leads to a reduction of the probability of correct recommendation (PCS) by at most 8% in scenarios with MTC being in the middle of investigated range while the PCS is increased by at least 12% in scenarios with MTC located close to the control. The question of sensitivity to prior parameters distribution is also studied. It is found that the randomization overcomes the fitting many parameters problem."

2. Elizabeth Pilling (Early Clinical Development IMED, AstraZeneca): "Challenges in Combination Trials in Oncology"

"The challenges in the design, methodology and interpretation of combination trials in Oncology are varied. This talk will illustrate examples and experiences across a number of trials, encompassing dose escalation, dose expansion and randomised studies. Key challenges that will be considered will include:

- Dose escalation methods such as the Continuous Reassessment Method are well established. This methodology can be utilised for combination studies where the dose of only one component of the combination is varied. However further work is required for methods where the dose of two of the components is varied.
- Choice of starting dose for each component.
- Decisions based on safety where events are expected from more than one component e.g. risks with drawing conclusions from dose escalation data from small numbers of patients where dose limiting toxicities may be observed from individual components.
- Decisions about dose selection when there may be other confounding factors e.g. a relevant biomarker.
- Allowing both dose and schedule to be varied. An example of how this information is incorporated using modelling will be illustrated.
- Drawing conclusions from small amounts of single-arm data in dose expansions.
- Strategy for individual component testing in randomised trials and the need for early planning of the whole development path of the combination. Factorial Experimental Design will be considered to explore optimal conditions or other methods to explore the design space, dose range finding trials to robustly explore different doses, and doing randomised trials earlier in development to inform decision making.

3. Alun Bedding (Roche): "Innovative statistical approaches to combination studies in anti-infectives"

Combination trials tend to be seen as the pre-dominance of oncology; however, in other therapeutic areas they have many benefits. The treatments for many viral diseases are effective and safe, however, in some there is still a clinical unmet need. Levels of successful vaccination have reduced the need for treatments in some viral diseases, however, where there is a need, current therapies show low efficacy and poor tolerability. Monotherapies are seen to be partially effective, however, it is thought that combinations would provide better efficacy, whilst still maintaining a good safety profile.

The development of combinations in anti-virals relies more on combining two new molecular entities rather than adding onto an existing standard of care. This presents many problems; however, some learnings from oncology can help with the development of these combinations. In this presentation I will show how using a platform study, combined with Bayesian and adaptive methods will increase the chances of effective combinations coming to market. Platform trials, where many treatment arms are compared to a common control are seen as an efficient way of testing new therapies. The use of Bayesian stopping rules for futility allow for the stopping of ineffective arms. The use of borrowing also adds to the efficiency. These ideas may be coupled with the use of seamless Phase II/III designs to further increase efficiency in moving towards the registration of new combination therapies.

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Examples of Using Big Data

Speakers:

1. Jixian Wang, (Celgene): "A practical propensity score calibration approach to the analyses of observational studies with incomplete data"

"Observational studies, e.g. disease registries, are increasingly used to evaluate treatment outcomes in real world settings. Propensity scores (PS) have been commonly used to reduce or eliminate confounding in the evaluation. However, often some confounders are only measured in a subset of patients. Using only the subset ignores a large amount of information, while using confounders only available from all patients may be subject to confounding biases. Propensity score calibration (PSC) is a convenient tool to adjust the impact of incomplete data. Classical PSC methods are based on approximate measurement error (ME) models since the true ME model is complex. A recently proposed PSC approach does not need the ME model, hence is robust to model specification and approximation. However, the approach needs complex calculation, hence it is difficult to utilize standard model fitting procedures. We propose using Bayesian bootstrapping in combination with this approach. The proposed approach can be implemented in standard statistical software with minimum programming. Also, it can be applied to a wide range of models and model fitting approaches. A simulation was conducted to examine the properties of the proposed approach for a wide range of models. Simulation results showed that the proposed approach outperformed the approaches using all patient with a subset of confounders only and that using only a subset with all confounders, in terms of their variance, bias and mean squared error. It provided consistent estimates, with negligible estimated bias, and confidence intervals with approximately correct coverage."

2. Adam Jacobs (Premier Research): "Qualifying a cognition endpoint for use in multiple sclerosis by combining data from many clinical trials"

"The importance of cognitive function as a domain of disability in multiple sclerosis (MS) is increasingly being recognised. Two measures of cognitive processing speed, the paced auditory serial addition test (PASAT) and the symbol digit modalities test (SDMT) have been used to measure cognition as secondary outcome measures in MS trials. However, before sponsors can be confident of using such measures as primary outcome measures, they need to be reassured that such measures would be acceptable from a regulatory point of view.

The FDA has recently published guidelines of their "Clinical Outcome Assessment Qualification Program", in which they provide a mechanism for submission of data on qualification of outcome measures for use in clinical trials. If such measures are approved by the FDA, then sponsors can be confident of using them in clinical trials. In this presentation, I shall describe the analyses used for qualification of cognition measures in MS trials, based on analysis of a combined dataset of 14 MS trials including over 12,000 patients. The data was acquired by the Multiple Sclerosis Outcome Assessments Consortium (MSOAC), which is funded largely by the National MS Society (grant # grant # G-1508-05893) and is managed through the Critical Path Institute (C-Path). Data was remapped by C-Path to the CDISC data standard for MS that was developed through MSOAC. The standardized, anonymized data was aggregated and subjected to quality control at C-Path. The placebo arms of this data base are available to qualified researchers."

3. Margaret Jones (UCB): "Extracting additional value from clinical data through collaboration"

Clinical development modernization efforts have become essential as clinical trials have experienced increased expectations, costs and design complexity. The utilization of historical clinical data can enhance drug research and development by refining study design, conduct and analysis. TransCelerate is leading a collaboration across 12 companies to share placebo and standard-of-care (PSOC) clinical data with the aim to enhance innovative drug product development by better informing clinical safety interpretation and trial design. Use cases include developing a standing safety cohort for providing context around serious adverse events observed in ongoing trials, and using data from prior trials to reduce the number of patients in new proof of concept trials. This discussion will cover use cases for the shared PSOC data, challenges around data sharing, successes to date, and important patient benefits. The TransCelerate PSoC database is operational and contains data from dozens of trials (as of November 2016) across multiple TransCelerate member companies. For purposes of the PSoC database, Placebo data is defined as any data generated from a control arm of a trial whereas the subject received only an inert substance. Standard of care data is defined as any data generated from a control arm of a trial whereas the subject received an active treatment.

Bayesian Methodology

Speakers:

1. Adam Crisp (GSK): "Use of "conditional assurance" to evaluate futility criteria and event targets in cardiovascular outcomes trials: an example using elicited priors"

In recent years, the use of "assurance" has become increasingly common as an alternative to power in helping sponsors assess a trial's overall probability of success (PoS). A key feature of assurance is that the likelihood of success is averaged over a prior distribution for treatment effect. While assurance estimates overall PoS it is of less value for trials with futility interims, since the degree of risk discharged by a futility interim is not identified. For example, the overall PoS might be low, but conditional on passing a futility checkpoint, the subsequent PoS might be high. As such assurance does not demonstrate the "option value" of futility interims. In this talk a framework will be presented for a hypothetical outcomes

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trial for which an elicited prior for the hazard ratio is available and a robust futility interim is planned. Group-sequential theory for the trial's operating characteristics conditional on a true treatment effect is combined with the prior to examine features such as the overall assurance, the probability of a Go at the interim and the probability of end-of-study success conditional on a Go at the interim (the "conditional assurance"). A cost/risk architecture can then be presented to decision-makers to support an informed assessment of the overall design. Example R code will also be shown for calculating the required levels of numerical integration via use of generic and tailored integration functions, using scale transformation of the prior as a key enabler for avoiding use of simulation.

2. Kimberley Hacquoil & Maria Costa (GSK): "Prior Elicitation: Teaching Old Dogs New Tricks"

At GSK, the demand from project teams to use Prior Elicitation to support discussions around clinical trial design is increasing rapidly. However, without the knowledge of statistical concepts used in the Elicitation process, the Experts will not be able to turn their own knowledge into a prior distribution that is usable and reflective of their beliefs. Training Experts for a Prior Elicitation session is therefore a critical piece to the overall success of this exercise. To increase efficiency and time spent on the actual elicitation itself, this time-consuming activity was an obvious candidate for an eLearning. Obvious - yes, but straightforward and easy - no!

This talk will address some of the challenges and pitfalls of how to create a fit-for-purpose eLearning for Prior Elicitation. A central part of an elicitation session is the interaction between the Experts and the Facilitator. Emulating this interaction in an eLearning environment poses a variety of challenges. The aim is for the Experts to understand and use statistical and probabilistic concepts without having a statistician responding to them (as they normally would in an elicitation training session). The balance between teaching concepts, using examples and testing the user understands the concepts needs to be appropriate to keep engagement and meet the objectives of the eLearning. Add in time constraints to the training and the result is a very stimulating and thought provoking assignment. A live demonstration of the finished eLearning will attempt to showcase the potential value of the tool for the industry.

3. Lisa Hampson (University of Lancaster): "Use of frequentist and Bayesian approaches for extrapolating from adult efficacy data to design and interpret confirmatory trials in children"

New medicines for children should be subject to rigorous examination whilst taking steps to avoid unnecessary experimentation. Extrapolating from adult data can reduce uncertainty about a drug's effects in younger patients meaning smaller trials may suffice. We consider how to design a confirmatory trial in children intended to compare the efficacy of a new drug, E, against control. Assuming that conduct of this trial is conditional on having demonstrated a significant beneficial effect in adults, we adopt a Bayesian approach to incorporate the adult data into the design and analysis of the paediatric trial. At each stage, inferences are made using all available data to update a Bayesian mixture model for prior opinion on the degree of similarities between adults and children. Using this framework, we propose designs for the paediatric trial which are specified by calibrating the sample size and final decision rule to: a) achieve a high frequentist power and high minimum (or average) Bayesian positive predictive value of a significant result in children; or b) ensure that a final decision to adopt (abandon) drug E in children is always associated with a minimum positive (negative) predictive value. Operating characteristics of our Bayesian designs are evaluated and compared with those of a recently proposed hybrid approach (Hlavin et al. Statistics in Medicine 2016; 35: 2117) where the sample size and significance level of a frequentist confirmatory trial in children are set to achieve a high frequentist power and high average positive predictive value of a significant result in children.

Oncology Methodology

Speakers:

1. Matthias Meller (Roche Pharmaceuticals): "Joint Modelling of Progression-free and Overall Survival"

"Progression-free survival (PFS) is a commonly used surrogate endpoint in oncology trials. To quantify the degree of the relationship to overall survival (OS) estimates of correlation coefficient as well as the survival function for OS are desirable. Fleischer et al. (2009) and Li and Zhang (2015), did use a latent-time illness-death model without recovery to jointly model PFS and OS and based on this model, derive parametric point estimates for the correlation betwee PFS and OS and the survival function of OS. They either assume exponential or Weibull transition hazards with a common shape parameter. We generalize their approach by omitting the latent time assumption and derive parametric and nonparametric point estimates as well as inference methods for the transition hazards, the correlation between PFS and OS, as well as the survival function of OS. We do this by relaxing the equal shape parameter assumption and under various assumptions on the stochastic process underpinning the multistate model, namely time-homogeneous and non-homogeneous Markov as well as non-Markov. Our results shed light on the implicit assumptions in Fleischer et al (2009) and Li and Zhang (2015). The methods are illustrated using a large Phase 3 oncology clinical trial.

Literature:

Fleischer, F., Gaschler-Markefski, B. and Bluhmki, E. (2009). A statistical model for the dependence between progression-free survival and overall survival. Stat. Med. 28 2669-2686.

Li, Y. and Zhang, Q. (2015). A weibull multi-state model for the dependence of progression-free survival and overall survival. Statistics in medicine 34 2497-2513."

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2. Jose Jimenez (Politecnico di Torino): "Cancer phase I trial design using drug combinations when a fraction of dose limiting toxicities is attributable to one or more agents"

Drug combination trials are increasingly common nowadays in clinical research. However, very few methods have been developed to consider toxicity attributions in the dose escalation process. We are motivated by a trial in which the clinicians able to identify certain toxicities that can be attributed to one of the agents. We present a Bayesian adaptive design in which toxicity attributions are modelled via Copula regression and the Maximum Tolerated Dose(MTD) curve is estimated as a function of model parameters. The dose escalation algorithm uses cohorts of two patients, following the Continual Reassessment Method (CRM) scheme, where at each stage of the trial, we search for the dose of one agent given the current dose of the other agent. The performance of the design is studied by evaluating its operating characteristics when the underlying model is either correctly specified or miss-specified. We show that this method can be extended to accommodate discrete dose combinations.

3. Iftekhar Khan (Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick): "Extrapolation of Utilities Between Disease Progression and Death in Cancer Trials for Economic Evaluation"

Introduction: In cancer trials, health related quality of life (HRQoL) are often collected until disease progression (PD). For health economic evaluation, EQ-5D utility data is required beyond disease progression. Assumptions made about the behaviour of utility data between PD and death are unrealistic and criticised by re-imbursement authorities. Extrapolation of EQ-5D beyond PD has not been used, although extrapolation this is commonly used for survival data. We demonstrate the feasibility of extrapolation of utilities beyond PD for the purposes of estimating quality adjusted life years (QALYs). Methods: Data from 100 lung cancer patients followed up for at least 12 months were used to extrapolate EQ-5D-3L utilities after PD. Several non-linear models were postulated including a Lorentz, Rational, 5-Parameter, Pareto, Exponential and Linear models. Extrapolation of survival times were generated using a Royston-Parmar (3 Knott) flexible parametric survival model in order to estimate the QALY. Models were compared in terms of AIC and impact on QALY estimates.

Results: Utility extrapolation is feasible. The more complex 5-parametermodel appears to be the most useful (lowest AIC value of 92.4) in terms of predictive ability beyond 12 months. Two parameters were statistically significant ($p<0.001$). The Lorentz, Rational and 5-parameter models generated the most accurate estimates of mean PP utilities and QALYs: 0.474 vs. 0.508, 0.509 and 0.487 respectively for utilities; and 3.176 vs. 3.37, 3.37 and 3.26 for QALYs.

Conclusions: Modelling post progression utilities as well as extrapolation of utilities beyond the study follow up appears feasible and is an alternative to mapping or using published utility estimates.

Innovative Approaches to Rare Diseases

Speakers:

1. Simon Wandel (Novartis Pharma AG): "A Bayesian single-arm study design accounting for uncertain historical control rates"

"Paediatric cancer drug development is challenging. Children are a particularly vulnerable population, and many childhood cancers are rare. Therefore, often single-arm studies are conducted. These compare the efficacy of the novel treatment to a (fixed) historical control rate. While this approach is popular, it is problematic from a statistical perspective, since it ignores various sources of uncertainty, including the between-study variability and potential bias. It is therefore important to consider alternative approaches for single-arm studies.

We will discuss a Bayesian study design that uses the predicted historical control rate to benchmark the novel treatment against control. The prediction is done within a meta-analytic framework1, 2 that accounts for the between-study variability. In this framework, the prior distribution for the between-trial heterogeneity is critical, especially when only few historical studies are available3. This design aspect, but also design metrics such as operating characteristics are important when planning the study and will be discussed specifically. We will illustrate the design with a case study in paediatric high-grade glioma (HGG), a rare disease with an estimated yearly incidence of 0.85/100'0004,5. The study evaluates a novel combination treatment using response rate as the primary endpoint. We will show how reflecting the uncertainty helps to improve decision making as compared to a study using a fixed historical control rate.

1. Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. Clin Trials. 2010

2. Schmidli H, Gsteiger S, Roychoudhury S et al. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics 2014

3. Friede T, Röver C, Wandel S, Neuenschwander B. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. Biom J. 2016

4. Fangusaro J. Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology. Front Oncol. 2012

5. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012.Neuro Oncol. 2015"

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2. Florence Le Maulf (PRA Health Sciences): "Case study: Would an enrichment design increase the chance of detecting a treatment effect in a study of patients with different types of rare Interstitial Lung Diseases?"

Background: A Phase III study was being designed to assess the effect of a new drug for treating patients with several types of rare Interstitial Lung Diseases. The primary endpoint was the annual rate of decline in forced vital capacity (FVC) and the sample size was based on detecting a reduction in the rate of decline in FVC with the new drug compared to placebo. Based on cohort studies, some patients with a specific disease pattern have a higher rate of FVC decline than patients without the pattern. It was suggested that enriching the study for those patients could increase the chance of detecting a treatment effect.

Methods: In order to assess the properties of an enriched design, research was done to assess the properties for different potential study designs using the following approach: - Literature/regulatory guideline search on the enrichment approaches, co-primary populations and possible multiplicity adjustments - Definition of design options (e.g. enrichment vs. no enrichment, Hochberg vs. Bivariate multiplicity adjustment, different enrichment proportions) - For each design, comparison of the power properties under different scenarios (e.g. assumed treatment effect and variability overall and in the enriched population). The presentation will cover the findings from this research on enrichment designs based on a real case study together with the work that followed on the implementation of an enrichment design including regulatory interactions.

3. Jixian Wang (Celgene): "Toward more flexible and practical multiple n-of-1 trial designs for small patient population"

"Multiple n-of-1 trials have been widely used to evaluate treatment effects when the patient population is small and large trials are infeasible. A well-designed crossover design can be used to compare treatment effects within patients efficiently. However, sometimes such designs with fixed sequences may have limitations in practice, e.g., a patient may be on an inferior treatment unnecessarily long, or frequent switching between treatment may not be feasible. We consider multiple n-of-1 trial designs that are more flexible and closer to clinical practices, in particular, designs allowing response-dependent treatment switching, e.g, switch at failure (SaF). In these trials, patients are randomized to multiple well designed treatment sequences, but only switch to the next treatment when the current one has failed. These designs are not as efficient as ordinary crossover designs, but they follow clinical practice when there is more than one treatment option. We show that the SaF designs can achieve multiple objectives including treatment comparison within and between patients, individual treatment selection and selection of the optimal test treatment sequence and treatment strategy. The SaF designs can also be enriched by adding, e.g., sequential randomization at failure. For analyses, in addition to the common mixed models based approaches, analysis of total response periods, time to failure and inverse probability weighting may also be used. The designs and analyses are illustrated by an example under a real scenario and their performance are compared with the fixed sequence crossover design."

Regulatory Hot Topics

Speakers:

1. Nicholas Latimer (University of Sheffield): "Adjusting for treatment switching in randomised controlled trials – methods, performance and acceptance in health technology assessment"

Adjusting for treatment switching in randomised controlled trials – methods, performance and acceptance in health technology assessment. Estimates of the overall survival benefit of new cancer treatments are often confounded by treatment switching in randomised controlled trials (RCTs) – whereby patients randomised to the control group are permitted to switch onto the experimental treatment upon disease progression. In Health Technology Assessment (HTA) estimates of the unconfounded overall survival benefit associated with the new treatment are needed. Several switching adjustment methods have been advocated in the literature, some of which have been used in HTA. Simulation studies have provided evidence on when adjustment methods are likely to perform well, and when they are not likely to be appropriate. However, decision-makers around the world exhibit varying degrees of reluctance to use adjustment analyses. In this talk we review adjustment methods such as the Rank Preserving Structural Failure Time Model (RPSFTM), Inverse Probability of Censoring Weights (IPCW) and two-stage adjustment. We consider evidence on their performance, their limitations, and the remaining barriers to more widespread acceptance of analyses resulting from their application.

2. Anja Schiel (Nowegian Agency (Unit for HTA & Reimbursement)

Due to the ever increasing pressure to get promising drugs to patients early, trials unfortunately are designed with limited follow-up and in addition might be terminated early. Time-to-event data have been a backbone of trials in the past, yet their usefulness is lost if only very limited numbers of events are observed and data remain immature. Regulators and HTA agencies both have recognized the problem with increasing uncertainty and the consequences this has on regulatory and reimbursement decision making.

While regulators have generally relied on conventional well established analyses of time-to-event data, in the field of HTA due to the specific requirements of pharmacoeconomic modelling, methods such as parametric estimation have gained increasing popularity. The presentation will address the assumptions those estimations are based on, the caveats of their use and their potential to contribute to better informed decisions.

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3. Lisa LaVange (Statistical Policy and Guidance at FDA)

The consistent application of statistical policy across therapeutic areas in the Center for Drug Evaluation and Research (CDER) at FDA is essential for high-quality reviews and also aids in achieving transparency about our expectations for industry. The clear articulation of those policies through issuance of statistical guidance documents can further contribute to more efficient and successful drug development programs. I will describe our process in the Office of Biostatistics for identifying areas or topics where statistical guidance is needed and provide an overview of past and current statistical guidance documents in CDER. I will also review some of the comments we received from the public docket on our most recently published guidance, Multiple Endpoints in Clinical Trials, and talk about the motivation for issuing a new draft guidance on adaptive designs in lieu of finalizing the 2010 draft guidance. Finally, I will discuss the statistical guidance documents included as commitments in the 21st Century Cures Act and the Prescription Drug User Fee Act (PDUFA) VI.

4. Armin Koch (Hanover Medical School)

ICH-E17 was primarily intended to promote the conduct of multi-regional clinical trials as the primary source of evidence for substantiating efficacy and safety of a new drug, or a known drug in a new indication. The idea that one trial then should form a sound basis for decision making in various regulatory regions, however, leads to a number of interesting problems regarding the need to agree on aspects of design, the role of the assessment of consistency of outcome across regions, and the discussion of minimum requirements regarding information per region. The presentation will provide an overview on these aspects and summarizes some of the comments from the discussion.

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1. Bootstrap Survival Analysis using Historical Control Data in a Life-threatening and Ultra-rare Disease

Clare Elkins (Alexion Pharmaceuticals)

A disease is generally considered to be ultra-rare if it affects one patient per 50,000 people and most ultra-rare diseases affect far fewer than this - as few as one per million or less. When designing studies and performing analyses that deliver therapies for life-threatening and ultra-rare diseases, there is usually no opportunity to evaluate survival data against a contemporary, concurrent dataset. We will present a bootstrap survival analysis that matches historical control patients to treated patients by key risk factors. For each treated patient a match was identified among the historical control patients by randomly selecting from the historical controls subset with corresponding risk factor(s). Once a historical control match was identified for each treated patient, Kaplan-Meier survival statistics comparing treated and control patients were obtained using this set of controls. This process was repeated to obtain a bootstrap estimate of the variability associated with the survival rates in the historical control group as well as the log-rank test p-values. These results show that when matching historical control patients with treated patients by key risk factors and conservatively selecting matches that survived at least to the age of the treated patient, the survival curves differed between treated and controls with better survival among treated patients.

2. A Practical Application of Multiple Imputation (MI) in a Double Blinded Randomized Phase III Study in Spinal Muscular Atrophy

Richard Foster (Biogen)

In a double blinded randomized phase III study in subjects with later onset spinal muscular atrophy (SMA), MI was pre-specified as the primary method for handling missing data at both the interim and the final analyses. It was also planned that the interim analysis would be performed on the ITT Set thus necessitating imputation for all ongoing subjects. The advantages (such as the increased power at the interim analysis) and the challenges (such as choosing the optimal timing for interim analysis and method for determining the alpha level at the final analysis) will be described both based on simulated and actual trial data.

3.Simulation of multiple endpoints and investigation of multiple endpoints in a clinical trial.

Aiden Flynn (Exploristics)

A novel antibacterial treatment for a severe gastrointestinal condition is to be evaluated from an early phase. Based on the limited biochemical information available traditional approaches suggest a prohibitively large sample size requirement for phase 2b/3 studies. It is desirable to design a staged investigation that maximises the likelihood of a successful trial while minimising the economic impact of a failure.

A number of correlated relevant endpoints are considered jointly including clinical cure, reduced bacterial load, time to resolution of diarrhoea and mortality. All study objectives were evaluated for parallel groups RCT and single group design versus a clinically relevant (historical) threshold. The KerusTM clinical trial simulator was used to simulate multiple endpoints and compare alternative approaches for assessing efficacy, here defined as non-inferiority in clinical cure and superiority in another endpoint. These studies were performed in a framework with multiple interim analyses thus providing regular feedback on study progression. Using these multiple scenarios, simulations covered a range of plausible effect sizes based on real-world health records with historical and live data. The likelihood of meeting non-inferiority and superiority objectives, individually and jointly, were calculated for each scenario. We indicated that if early biochemical results are accurate a substantially reduced and feasible sample size can achieve enough power in multiple objectives that allow investigation in a broader population. Further, we demonstrated that if the early biochemical results were over-optimistic it would be possible to identify the problem early and abort development with minimum economic loss.

4. Use of a composite criterion taking into account rescue medication intake in an orphan disease with a seasonal pattern

Maëva Dupuis-Deniaud (MDSTAT Consulting)

The Vektis study, a phase III, international, double-masked, vehicle-controlled trial, evaluated the efficacy and tolerability of ciclosporine cationic emulsion 1mg/ml eye drops for treating active severe vernal keratoconjunctivitis in paediatric population. This study, ended in 2016, was designed to show the superiority of the active drug versus its Vehicle, as no reference drug exists in the severe cases of the disease. In order to overcome regulatory, disease and ethic constraints (i.e. effectiveness over the whole allergic season and not only at a specific timepoint, need for corticosteroids rescue therapy to address ethic concern in the vehicle group and that cannot be used as covariate, and possibility of corneal ulceration), we used as main endpoint a composite criterion, based on 3 components : the Oxford scale measuring keratitis, the number of rescue medication courses and the occurrence of corneal ulcers. The last two criteria were used as penalties with increasing the Oxford scale of one point (worsening) per rescue course or occurrence of ulcer. The data of a previous study were used to estimate the effect size and to calculate the sample-size for the Vektis study. The composite endpoint was discussed with both the paediatric committee and Scientific Advice Working Party of EMA and endorsed under the condition that results on the composite endpoint and on each component be consistent. As expected the result was mainly driven by the Oxford scale but the use of rescue medications in favour of the drug increased the difference between the treatment groups.

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5. Application of Monte Carlo simulation to relative survival and beyond

Mansour Sharabiani (PHD, Senior Statistician Royal Marsden NHS Trust)

Background: Relative Survival (RS) compares observed survival probability of a group of subjects, (e.g., cancer patients), with survival of a "similar" cohort using population based Life-Tables. Existing methods provide closed-form equations to estimate RS. We propose application of Monte Carlo (MC) simulations toRS, which provides additional capacities including hypothesis testing.

Materials & Methods: UK's population mortality probabilities were extracted from Office of National Statistics' Life-Tables for corresponding children (N=137) with Differentiated Thyroid Cancer (DTC) from Royal Marsden according to their gender, age, and year of diagnosis. Extracted probabilities were used to generate 1000 time-to-event Monte Carlo (MC) simulations per DTC child. Actual DTC children's follow-up data, obtained from patients' hospital files, were compared to the time-to-event simulated data using survival percentile, Kaplan-Meier survivor function, Log-Rank test, and Cox-regression.

Results & Conclusion: Overall, DTC patients had statistically significantly lower survival than general population. Methodologically, the proposed simulation-based approach presents significant practical and conceptual advantages over alternative methods of closed-form equations for RS. Practically, simulated data can be fed into various statistical packages, e.g., R, Stata, and SPSS. Conceptually, simulated population can be given as input to all survival-based statistical models, and the scope of analysis can go beyond RS toLog-Rank test, Cox model, non-parametric survival models, and so on. Moreover, MC simulations can easily incorporate potential uncertainty in calculation of Life-Table probabilities.

6. Bayesian methods for leveraging existing clinical data in paediatric trials

Nicky Best (GSK)

Paediatric populations present several challenges and opportunities for clinical trial design and analysis, due to practical and ethical constraints on sample size. Both the EMA and FDA have held public workshops recently to discuss ways of leveraging data from adults or other paediatric populations to inform regulatory decision-making for paediatric medicines. In this talk, we will share our experiences of two planned GSK paediatric trials where we are proposing a Bayesian approach to incorporate existing data on the treatment effect from adult trials and other relevant historical studies. We will show how use of a robust Bayesian mixture prior (Schmidli et al 2014) – which combines the historical data with a flat (non-informative) component – allows for adaptive down-weighting of the historical data as a function of the degree of conflict with the new trial data. Clinical trial simulation results comparing some of the operating characteristic of the Bayesian design with conventional Phase 3 designs will be presented and we will outline how we addressed regulatory requests to provide an explicit statement of the strength of prior assumptions, and clarity over relevance of prior information to paediatric target population.

7. Applying Bayesian stopping rules to a pilot study with rare disease

Komel Khabra (Royal Marsden NHS Foundation Trust)

Background: A pilot phase II trial evaluating 5-fluorouracil (5FU) in children and young adults with relapsed ependymoma who have received previous radiotherapy was set up. Since this is a single-centre pilot study in a rare disease, sample size was limited to 15 patients. Primary endpoint is response rate at end of 6 cycles of treatment. Investigators wanted some indication that 5FU shows efficacy during the trial and whether it is worth carrying on recruitment. Methods Initially a Simon two-stage design (expected response 30%, and <20% is unacceptable) was explored; however it required >15 patients. Therefore a Bayesian approach was considered keeping number of patients fixed (n=15), with prior of beta distribution (parameters: alpha=5, beta=18) based on evidence from previous studies. Posterior probabilities that the true response is at least 20% were investigated over all possible number of responses at planned interims after 5 and 10 patients. Based on clinical decisions (no standardised medical treatment available in this indication), posterior probability of 0.3 was chosen as cut off at each interim for decision making as to whether study recruitment should continue.

Results: The calculations implied 0 out of 5 patients to respond at first interim, at least 1 out of 10 at second interim to continue recruitment and at least 2 out of 15 patients at end to trigger further investigation.

Conclusion: The Bayesian method allowed keeping the fixed number of patients. This may be applied when a disease is rare and stopping rules are required to stop for any futility.

8. Bayesian Prior's Essential Role in Innovative Trial Designs for Rare Diseases Drug Development

Penling Sun (Rare Disease Research Unit, Pfizer, Inc)

The nature of rare diseases has been seriously challenging Frequentist-based conventional approaches for designing clinical trials, be it to choose realistic sample sizes, aim at right study populations, select proper endpoints, or estimate & harness accurate recruitment rate. Devising Bayesian priors through carefully collecting, assembling, and quantifying natural history data, and letting it guide clinical trial design innovations, may essentially tackle such challenges effectively. This presentation will first explain the rationale as well as the principles of forming compelling Bayesian priors in rare diseases setting, and then illustrate in-depth how the Bayesian priors can guide innovative (adaptive) trial designs to optimize the probability of trial success. We will also present a real-world example of an orphan neuromuscular disease clinical trial, which would concretely demonstrate the Bayesian approach's strategic advantages in significantly reducing sample size, accurately identifying the most preferable study population, and, ultimately, maximizing the asset's Return-on-Investment (ROI).

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9. Evaluation of Bayesian Belief Networks to estimate probability of technical success of phase III clinical trials

Wilmar Igl (AstraZeneca)

Background: Business decisions in the drug industry depend on multiple factors with uncertainty. These uncertainties are especially important when making the decision whether to launch an expensive phase III trial. However, not only more objective quantifiable risks, egstatistical power, but also more subjective, but quantifiable risks, e.g. strength of the biological model, are of crucial importance. Therefore, we evaluated Bayesian Belief Networks (Fenton & Neil, 2013) as quantitative models to represent the evidence to estimate the probability of technical success (PTS) of phase III trials.

Method: We performed literature search and conducted semi-structured interviews to identify the model structure. We developed a survey to elicit a priori and a posteriori PTS and relevant factors related to historical phase III trials. We collected survey data from product statisticians at AstraZeneca. The survey data was used to parametrize the Bayesian Belief Network and make it usable as predictive model for future phase 3 trials. The model was implemented using the AgenaRisk software, which uses a variation of a propagation algorithm to update the conditional probability tables using Bayes theorem (Agena, 2017a,b).

Results: The development process of the PTS estimation model will be described including the final survey and model. The model includes the top nodes “Basic Support”, “Design Support”, “Design Risk Support”, and “Drug Development Quality Support” and multiple parent nodes. The parametrization of the model and its performance for prediction will be demonstrated using simulated data.

Conclusion: Bayesian Belief Networks may be a useful quantitative tool to support business decisions.

10. The Value of Different Strategies for a Phase II/III Program

Robbie Peck (University of Bath)

My PhD project concerns the optimisation of the drug development process at a program level. This involves considering multiple phases of treatment refinement and dose selection together. While individual phases of drug development have been studied in depth, there has been relatively little work that looks at two or more phases jointly. I use numerical computations and simulations to model different programs and use a form of gain function, or “net present value”, in order to both study optimal decision making throughout phases, and to quantify the value different statistical methods bring to a program.

Optimal decisions can be made by evaluating the expected value of a gain function conditional on posterior beliefs about treatment effect gained from Phase II data. Embedding these optimal decisions in a combination test and using group sequential methodology can produce programs with impressive properties.

11. Evaluating the Overall Performance of Bayes Optimal Adaptive Enrichment Designs

Thomas Burnett (University of Bath)

We use a Bayesian decision framework to optimise the choice of patient population at the interim analysis of Adaptive Enrichment trials. For example we may choose to recruit the rest of the sample from: the same population as the first part of the trial, a sub-population, or the trial may be stopped early for futility. Bayesian methods are only applied at the interim analysis to select the population, the final hypothesis testing uses frequentist methods to ensure strong control of the Familywise Error Rate. Under the Bayesian decision framework we may also evaluate the overall performance of trial designs. Using simulation we compare Bayes optimal Adaptive Enrichment trials with some fixed sampling alternatives, this shows where the adaptive design may offer benefits in practice. We examine a range of scenarios varying the size of the sub-population, the total available sample size and prior beliefs about the treatment effects in each population. This method of optimisation is very flexible, if we can evaluate the expected future behaviour of the trial we can find the optimal decisions. For example we can: add more sub-populations (these must be pre identified for the hypothesis testing), add more interim analyses or use more complex data types such as survival endpoints or longitudinal observations.

12. A simple way to unify Multi-Criteria Decision Analysis (MCDA) and Stochastic Multi-criteria Acceptability Analysis (SMAA) using a Dirichlet distribution in benefit-risk assessment

Gaelle Saint-Hilary (Dipartimento di Scienze Matematiche (DISMA), Politecnico di Torino)

Quantitative methodologies have been proposed to support decision-making in drug development and monitoring. In particular, Multi-Criteria Decision Analysis (MCDA) and Stochastic Multicriteria Acceptability Analysis (SMAA) are useful tools to assess the benefit-risk ratio of medicines according to the performances of the treatments on several criteria, accounting for the preferences of the decision-makers regarding the relative importance of these criteria. However, MCDA requires the exact elicitations of the criteria weights by the decision-makers, which may be difficult to achieve in practice. SMAA allows for more flexibility and can be used with unknown or partially known preferences, but it is less popular due to its increased complexity and the high degree of uncertainty in its results. We propose a simple model as a generalization of MCDA and SMAA, by applying a Dirichlet distribution to the weights of the criteria and by making its parameters vary. This unique model permits to fit both MCDA and SMAA, and allows for a more extended exploration of the benefit-risk assessment of treatments. The precision of its results depends on the level of confidence of the decision-makers in their elicitation of preferences, and its interpretation is easier than SMAA and understandable by non-statisticians.

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13. dECiDe: software developed by Cytel and AstraZeneca for early clinical study design

Dominic Magirr (AstraZeneca)

In Early Clinical Development at AstraZeneca we apply a consistent statistical approach to go/no-go decisions (Frewer, 2016). We choose a key endpoint, or possibly two key endpoints, and the sample space for the corresponding point estimate is split into three zones: red, amber and green. The amber zone represents inconclusive evidence, where our senior leaders must use their overall impression of the data, as well as factors external to the trial, to come to a final decision. Decision criteria are pre-specified by the clinical team at the design stage. Our job as statisticians is to communicate the uncertainties and risks associated with various options. To simplify this task, we have worked with Cytel to develop a software tool called dECiDe, which performs the necessary calculations and produces relevant tables and figures. Outputs have a consistent format that can be presented to senior leaders at internal governance bodies. It is sometimes helpful to quantify uncertainty in frequentist terms, and we will often need to assess the impact of interim analyses on the trial's operating characteristics. At other times we naturally make Bayesian probability statements, and may wish to formally combine evidence from different sources. dECiDe gives us flexibility to do all of this.

14. Re-engineering Early Drug Development

Maria Costa (GSK)

Historically, hypothesis test type approaches dominated drug development, even within the early phase stages. This was also the case at GSK, where frequentist inference and pair-wise comparisons were used as the default approach. More recently much has been said about the importance of using early phase clinical trials, particularly Phase 2, to learn about the performance of a drug on relevant clinical endpoints. With this in mind, a group of statisticians and pharmacokineticists at GSK set out to develop and implement a cross-functional transformational initiative, Re-engineering Phase 2, with the aim of making Phase 2 studies at GSK more efficient and better equipped to answer the questions of real interest. This initiative focused on four areas: Bayesian predictive inference and futility assessment, model-based dose-response, use of historical data, and quantitative peer review. This talk will describe each of these initiatives, including how key hurdles were overcome, providing case studies and highlighting some of the challenges with implementing this approach across the entire R&D organisation.

15. On the use of pre-clinical information in phase I dose-escalation trials

Haiyan Zheng (Lancaster University)

Bayesian model-based approaches are increasingly important in designing phase I dose-escalation trials, where the principal aim is to estimate the maximum tolerated dose (MTD) of a novel compound. Conventionally, vague prior distributions are used for model parameters. However, information on the dose-toxicity relationship will be available from pre-clinical studies by the time first-in-man trials are conducted. If pre-clinical data are commensurate with dose-toxicity relationship in humans, incorporating them into prior will lead to more efficient dose-escalation and greater precision for estimating the MTD. Such advantages, however, must be balanced against the risk that more patients may be treated with excessively toxic doses in the case of a prior-data conflict.

We propose a Bayesian decision-theoretic approach, with which the degree of commensurability can be dynamically measured during the course of a fully sequential phase I trial. The pre-clinical data are used to make optimal predictions for whether patients would have dose-limiting toxicity (DLT) or not. These predictions are optimal in the sense of maximising the prior expected utility, by assigning a utility of 1 to correct predictions, 0 to incorrect predictions of no-DLT, and c ($0<c<1$) to incorrect predictions of DLT. At each interim analysis, the prior predictions are compared with accumulated actual outcomes. Dose recommendations rely on the posterior distribution that borrows strength adaptively from pre-clinical studies according to the assessed commensurability. Simulation demonstrate the proposed approach sensibly handles prior-data conflicts and leads to robust and competitive dose-escalation scheme, compared with the optimal benchmark design and other Bayesian adaptive methods.

16. crmPack's dual endpoint approach to jointly model safety and PD: Operating characteristics for a single-ascending dose-escalation study with a continuous biomarker response

Charles Warne (Roche)

The primary goal of first in human (FIH) studies is to assess the safety and tolerability of the investigational drug, which traditionally has led to single-ascending dose studies designed to estimate the maximum tolerated dose (MTD). While escalating towards the MTD is appropriate for oncology FIH studies in terminally-ill patients where toxicity correlates with efficacy, it may not make sense for drugs in other indications, such as auto-immune diseases, where often FIH studies are conducted in healthy volunteers and the optimal biological dose (OBD) is of more interest than the MTD. The OBD is the quantity of a drug that will most effectively produce the desired clinical effect while remaining in the range of acceptable toxicity. If the OBD is lower than the MTD, then it is safer and more relevant to learn about the effect of the drug in this region than to keep escalating towards more toxic, and potentially less efficacious, doses.

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The added benefit is that enrolment can stop early if sufficient precision has already been obtained around the OBD. This poster will investigate how the dual endpoint CRM model in the R package crmPack can support decision making for a dose-escalation FIH study in healthy volunteers where both safety and pharmacodynamic (PD) effects on a continuous biomarker are of interest, and the objective is to estimate the OBD. The results of simulations will be presented to explore operating characteristics of the dual endpoint CRM model across a range of dose-response profiles for safety and PD.

17. Bayesian two-stage design in phase II clinical trials with time-to-event endpoints

Mounir Aout (Hoffmann-La Roche Ltd)

Recent reviews suggest that the use of Progression-free survival (PFS) in phase II cancer clinical trials has shown greater potential to predict success in a phase III setting. Frequentist approaches to the design of phase II cancer trials yielding survival endpoints commonly employ a two-stage design that includes a single interim analysis, and are usually designed based on an exponential distribution assumption. However, this assumption is not fulfilled when cancer immunotherapies are used, as these agents may be associated with a delayed clinical effect, long-term survivor and therefore complex hazard functions, compared to cytotoxic agents from which patients usually derive early benefit. In addition, the rigid study design of frequentist approach can be difficult to follow exactly because the response has to be evaluated on a pre-specified fixed number of patients. To address these limitations, Bayesian designs with good operating characteristics are ideal for earlier phase trials as they allow for flexibility in trial conduct and take into account information that accrues during a trial to update the posterior probability of parameters accordingly. In this poster, we propose a Bayesian two-stage design with time-to-event endpoint in single arm phase II cancer clinical trials. We will consider various parametric distributions including exponential, Weibull, lognormal, log-logistic, Gompertz and generalized gamma to take into consideration different shapes of hazard functions. Decisions will be made using the posterior distributions. Operating characteristics based on intensive simulation analyses will be provided for the Bayesian designs and compared with extensions of the Simon's designs with time-to-event endpoints.

18. Comparison of Dose-Finding Methods in Phase-II Clinical Trials

Saswati Saha (University of Bremen)

Characterizing an appropriate dose-response relationship and identifying the right dose in a clinical trial are two main goals of early drug-development. The MCP-Mod is one of the pioneer approaches developed within the last 10 years which combines the modelling techniques with multiple comparison procedures to address the above goals in clinical drug development. The MCP-Mod approach begins with a set of potential dose-response models, tests for a significant dose-response effect using multiple linear contrasts and fits the best model based on modelling techniques. However, there is quite a possibility of model misspecification in this approach. The non-linear parameters for the candidate models need to be chosen a priori for the multiple contrast tests. This may lead to a loss in power and unreliable model selection as well as model fitting.

Motivated by the above shortcomings, we compare MCP-Mod with other dose-finding approaches that are more robust in dose-response shape detection. In our presentation, we will discuss three state-of-the-art approaches which assume a candidate set of parametric dose-response models and test the null hypothesis of no dose-response trend against the composite alternative that one of the candidate dose-response shapes is true. These approaches do not make prior assumptions about the model parameters and are therefore more robust compared to MCP-Mod approach. Our focus is to compare these approaches with regard to their ability to detect the dose-response trend, potential to select the correct model and accuracy in estimating the minimum effective dose in dose-finding studies in an extensive simulation study.

19. The Design of a Phase II Dose-finding Trial: A Case Study using MCP-mod

Beki Finch (Roche)

Selecting an adequate dose at Phase II to take forward to Phase III is an important part of drug development. The incorrect dose could lead to late failures during Phase III. Often pair-wise comparisons to placebo are performed for the dose selection, but the success of this approach relies heavily on the doses chosen for testing in the Phase II trial. This poster will present a real-life example of a three-part Phase II study designed with the purpose of assessing both proof of concept and the dose-response using MCP-mod methodology.

20. Modelling of Renal Function and Drug Clearance A novel primary analysis approach for renal/hepatic impairment clinical pharmacology studies

Katie Patel (Roche)

Case Study: Modelling of Renal Function and Drug Clearance, A novel primary analysis approach for renal/hepatic impairment clinical pharmacology studies. The case study followed a conventional study design, with 6 volunteers planned to be enrolled into each of four renal impairment groups (normal renal function, mild, moderate and severe renal impairment). The conventional primary analysis for such a study would be group-level comparisons of each of the renally impaired groups versus the normal renal

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function group, based on the geometric mean ratio for the primary pharmacokinetic endpoint and the 90% CI. For this study, an innovative approach to the primary statistical analysis was employed by direct modelling of measures of drug clearance vs. measures of renal function using data from all volunteers. A comparison of the two approaches is presented..

21. Carrying forward informed decisions: Missing data in early phase studies

Thomas Brown (Veramed)

Early phase studies are often accompanied with multiple objectives related to dosage, safety, and pharmacokinetics/pharmacodynamics. However, these studies are typically powered to examine a single primary objective, leaving an increased risk for multiple secondary endpoints to be substantially underpowered. Once missing data arises on these outcomes, it becomes increasingly difficult to make informed decisions that can carry over to later phase research. Limited sample sizes that are often seen in these studies make the appropriate treatment of missing data even more critical. This presentation aims to provide guidance and introduce innovative techniques for handling missing data specifically for an early phase context; such that multiple objectives can be adequately assessed. Inappropriate techniques for handling missing data are used all too often, providing results that are unable to address the real question of interest. Part 1 of the presentation will look at two commonly used methods, last observation carried forward and multiple imputation, and use both real world and simulated data to examine under what scenarios such methods are valid for addressing the endpoints of interest. In the second part, pattern mixture models in multiple imputation will be discussed to examine how underlying untestable assumptions of a multiple imputation procedure can be explored to model various early phase endpoints. It will be shown that effective multiple imputation is highly dependent on a well-structured sensitivity analysis for valid inferences to be made.

22. Some tools to help you plan and analyses clinical trials with incomplete or missing data from DIA Scientific Working Group for Missing Data

Michael O'Kelly (Quintiles)

The DIA Scientific Working Group (SWG) for Missing Data started in Jan2012 and its members – from industry, academia and regulatory bodies – have made available a treasure house of software and training materials for trialists trying to take into account missing or unusable data. Training that can be downloaded includes three short courses by experts who are members of the group. The SWG even has template SAP text that includes explanations of the implications of a choice of missing data approaches. This template text has been reviewed by leading academics and practitioners who have used the approaches in real clinical trials. The icing on the cake offered by the SWG consists of over a dozen pieces of software shared by pharma companies and contract research organizations, that allow statisticians to implement new improved methodologies quickly and easily, that take into account missing or unusable data. Of the software available, one uses the R language, and the rest are SAS macros. Most of the software is very user-friendly, with extensive error-checking. This poster gives an introduction to the SWG and its work, describing the training materials and templates available. We will also highlight which estimands are targeted by the different methods/macros.

23. Some tools to help you plan and analyses clinical trials with incomplete or missing data from DIA Scientific Working Group for Missing Data

Michael O'Kelly (Quintiles)

The DIA Scientific Working Group (SWG) for Missing Data started in Jan2012 and its members – from industry, academia and regulatory bodies – have made available a treasure house of software and training materials for trialists trying to take into account missing or unusable data. Training that can be downloaded includes three short courses by experts who are members of the group. The SWG even has template SAP text that includes explanations of the implications of a choice of missing data approaches. This template text has been reviewed by leading academics and practitioners who have used the approaches in real clinical trials. The icing on the cake offered by the SWG consists of over a dozen pieces of software shared by pharma companies and contract research organizations, that allow statisticians to implement new improved methodologies quickly and easily, that take into account missing or unusable data. Of the software available, one uses the R language, and the rest are SAS macros. Most of the software is very user-friendly, with extensive error-checking. This poster describes the software that is available on the SWG's web site that uses multiple imputation to implement both missing-at-random and missing-not-at-random assumptions in continuous variables.

24. Some tools to help you plan and analyses clinical trials with incomplete or missing data from DIA Scientific Working Group for Missing Data

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approaches. This template text has been reviewed by leading academics and practitioners who have used the approaches in real clinical trials. The icing on the cake offered by the SWG consists of over a dozen pieces of software shared by pharma companies and contract research organizations, that allow statisticians to implement new improved methodologies quickly and easily, that take into account missing or unusable data. Of the software available, one uses the R language, and the rest are SAS macros. Most of the software is very user-friendly, with extensive error-checking. This poster describes a variety of software that is available on the SWG's web site, with applications for recurrent-event data, for doubly robust estimation, and for selection modelling.

25. Analysis of longitudinal health-related quality of life data – what is the impact on trial results of ignoring missing data?

Kim Cocks (Adelphi Values & University of York)

Aim: Oncology trials collecting patient-reported outcome (PRO) data have missing data due to death, disease progression or early recovery. Analyses ignoring this informative missing data may be misleading but analyses accounting for it can be complex and require strong assumptions that cannot be tested. Current guidelines for assessing the quality of a PRO study stipulate the statistical methods for handling missing data are explicitly reported but the choice of analysis method is not scrutinized. This review explored whether analysis methods can change the significance of treatment effects and therefore whether choice of analysis method is therefore an essential measure of quality.

Methods: Medline (Ovid) was searched from 2002 to 2014 for oncology randomised controlled trials reporting longitudinal PRO analyses. Papers using multiple methods with different missing data assumptions were included in order to compare results across methods. Level of attrition by treatment was extracted along with statistical analysis methods and results.

Results: Nine papers met the search criteria. Methods accounting for non-ignorable dropout altered trajectories over time but statistical significance between treatment groups using MAR model was generally robust unless there was substantial differential attrition between the treatment groups.

Conclusion: A repeated measures mixed model (MAR) appears to be robust when comparing treatment groups with similar attrition. Analysis of changes over time and the presence of differential dropout require methods accounting for non-ignorable dropout in order to fully interpret the data. The suitability of the analysis method should be added as a criterion for assessing the quality of PRO studies.

26. Joint modelling of On-treatment and Off-treatment observed data.

James Roger (Livedata)

The proposed addendum to ICH E9 on estimands and the associated comments from regulators is leading to the continued collection of efficacy data after the cessation of randomized treatment. Implicit in a treatment policy estimand is that outcome at final visit should be compared between arms regardless of the treatment chosen after randomized treatment withdrawal. However some of the follow-on data will be missing due to trial withdrawal. One possible way forward is to impute these missed off-treatment data. This poster explores the fitting of Bayesian models to the observed data both on and off randomized treatment. Multiple imputation can then be used, drawing parameter estimates from the posterior and using these to impute further off-treatment data in those who have withdrawn from the trial. In extreme, some patients will only have on-treatment data but still require imputation of off-treatment data. As such, the joint modelling of on and off treatment data is essential. One major difficulty is choosing between flexible models with parameters that are badly estimated and over-simplistic models with well estimated parameters. However, unlike the classic missing data problem there will be at least some data to help assess model assumptions. Ignorability of the missingness mechanism at trial withdrawal will be assumed.

27. Using "off-treatment" data to estimate the de facto estimand in a randomised trial

Dawn Edwards (GSK)

Regulatory agencies are increasingly asking for study trial participants who discontinue or otherwise deviate from randomised treatment to be followed up in order to facilitate the estimation of the de facto treatment effect in superiority trials. We set out to explore how to perform the analysis for a continuous endpoint where data collection is continued in some, but not all, patients after discontinuation of randomised treatment: we call this off-treatment data. The work was motivated by the problem of writing a statistical analysis plan for a pharmaceutical trial. We consider several alternative multiple imputation methods that can be used. The methods vary in their use of earlier outcomes and treatment discontinuation time in the mean part and in their use of treatment discontinuation in the variance part. Different methods make different assumptions about the missing data, specifically about what observed data to condition on in order to justify a missing at random (MAR) assumption, and whether or not treatment discontinuation is considered to represent a treatment failure outcome; they also make different demands on the observed data. Simulation results to explore the performance of the methods will be presented and discussed.

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28. The blind leading the (un)blind: Conducting successful interim analyses

Chetan Mistry (Veramed)

Performing an interim analysis can be a logistical nightmare and is not for the faint hearted. As the project statistician you need to ensure you have a clear vision of the planning, execution and follow up activities involved in an interim. A simple but effective planning tool such as a process flowchart can be utilised to share your vision and gain the co-operation and backing of your study team which will lead to its successful implementation. Strong communication skills are needed to manage the expectations from stakeholders outside of the study team as you will be accountable for the delivery of all the required elements for the interim analysis within the stringent timelines. A process flowchart based on a double-blind, randomised Phase II Proof of Concept study will be used to illustrate the depth of detailed planning required to ensure cohesion between the (multiple) blinded and unblinded teams, highlighting the main challenges in the organisation of an interim analysis to successfully manage several moving parts whilst remaining blinded.

29. Expect the Unexpected: Not everything goes according to plan with Data Monitoring Committees!

Alan Phillips (ICON Clinical Research)

Data Monitoring Committees (DMCs) are independent groups of experts who conduct regular reviews of the research protocol, clinical trial data and statistical analyses. DMCs have a responsibility to both patients (in terms of safety) and to the sponsor (in terms of trial credibility). In this presentation, three case studies will be discussed where the decision madeby the DMC didn't always go according to plan. The implications of the decision from a statistical and operational perspective will be discussed, together with recommendations on how the issues can be prevented from re occurring in future trials.

The first case study will discuss a study where the stopping boundary at a planned interim analysis was crossed but the DMC decided to continue the study. Case study 2 reviews a study where not all patients were included in the interim analysis, and when the final analysis was performed after stopping for efficacy the inferences changed. The third and final case study will focus on sample size re-assessment by a DMC. For this study two interim analyses for sample size re-assessment by a DMC were planned, with different recommendations between interim analysis 1 and interim analysis 2.

30. Designing a Futility Interim of a Continuous long term Endpoint using Repeated Measures Analysis

Helen Spotswood (Roche)

A futility analysis for a Phase 3 study of tocilizumab in Systemic sclerosis was to be designed based on the continuous endpoint of change from baseline in modified Rodnan skin score. This longitudinal data was to be analysed at 24 weeks using a mixed model for repeated measures (MMRM). One option would have been to design the interim analysis based on data from those patients expected to complete to week 24 at the time of the futility interim. This approach would have used data from only a small proportion of individuals randomised into the trial and would have ignored any information (due to correlation between measurements across visits) about the Week 24 measurement from Weeks 8 and 16 from the most latterly accrued patients. To use all available data in the design, and therefore the analysis, rather than a completers approach, multivariate normal data across visits and endpoints was simulated using means, standard deviations, and correlations from a completed Phase 2 study. A monotone missing data pattern for withdrawals, as well as missing data due to an expected recruitment pattern was introduced to mimic various possible data snapshots. Repeated measures analysis of multiple interim and final simulated datasets, followed by a group sequential design was used to explore the operating characteristics of different stopping boundaries and timing of the interim. Importantly, this approach enabled the exploration of designs to be extended to two correlated endpoints, where both would need to be 'futile' in order for the study to be stopped.

31. Application of analyses to identify and characterize predictive properties of biomarkers and support the definition of a biomarker positive population based on recurrent events data

Mattis Gattlow (AstraZeneca)

This poster describes analyses aimed to assess and characterize the potential predictive properties of biomarkers related to a new treatment of severe asthma and to support the definition of a biomarker sub-population where the new treatment is expected to have enhanced efficacy. The intention of the analyses is to explore the data from a phase 3 asthma study and the identified biomarker and sub-population are planned to be formally tested in a second study. The primary endpoint of both these studies is the number of asthma exacerbations during 12 months of follow-up, which is commonly analysed using a Negative Binomial model. Several analyses will be performed, ranging from descriptive (e.g. forest plots based on partitions of the data) to more sophisticated and computationally

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intensive (e.g. the SIDES method [Lipkovich I, Dmitrienko A (2014) Strategies for Identifying Predictive Biomarkers and Subgroups with Enhanced Treatment Effect in Clinical Trials Using SIDES, Journal of Biopharmaceutical Statistics, 24:1], and Generalized Additive Models applied in a counterfactual setting for prediction and qualitatively visualizing the biomarker impact on the effect). When exploring the first study one needs to take care so that selection bias does not lead to overoptimistic expectations on the results of the second study. Therefore, we present a number of re-sampling based analyses that assess the robustness of the findings. The methods will be illustrated using simulations.

32. Assessment of model assumptions for the analysis of recurrent event data

Sven Schnaidt (Boehringer Ingelheim)

Recurrent event data is very common in clinical research across many therapeutic areas. Examples comprise recurrent strokes or exacerbations in different respiratory diseases. A frequently used approach for the analysis of such recurring events is to apply 'standard' time-to-first-event analysis methods like Kaplan-Meier plots and Cox-regression models. However, discarding information on subsequent events not only results in reduced power, but also ignores important information on the potential long-term influence of an active substance on the events of interest. On the other hand, methods for the analysis of recurrent events are generally based on stronger assumptions on the event generating process. In addition, there might be other factors (e.g. treatment changes after the first event) that might bias estimates. Therefore, it is of utmost importance to check model assumptions as well as properties of each method and select the model that fits best to the data at hand. Simulated as well as blinded data from a respiratory trial will be used to demonstrate how these model assumptions can be assessed. In particular, count models (e.g. Poisson and Negative Binomial model), Cox-models as well as Cox-model extensions (e.g. Andersen-Gill and PWP models) will be discussed. Furthermore, caveats that may arise during the assessment of model assumptions will be discussed. Among others, it will be shown that a separate analysis of gap times between two subsequent events might not be appropriate. Finally, recommendations for the assessment of model assumptions and properties as well as the analysis of recurrent event data itself are provided.

33. Estimating the effect of measurement error on study results, particularly with expert scores

Eddie Channon (Chirostate Statistical Consulting)

It is important to judge how well assessors can use subjective rating scales and sometimes this is done by a small validation study where subjects are assessed twice. Often measurement error (repeatability) is summarised by a correlation coefficient, coefficient of variation or % agreement but it is difficult to specify a threshold of acceptability. The alternative is to look at the influence of measurement error on results from the main study.

The proposed approach takes the idea of sensitivity analysis and considers what would happen if one assessor could observe the same subjects a very large number of times at each planned assessment in the main study. The probability distribution of errors is estimated by the validation frequencies. This simulation helps scientists who are keen to know whether the observed study data is correct (statisticians usually focus on inferences about a population). The possible study result give a range possible estimates of treatment effect from this one study. The 2.5% and 97.5% quantiles are described as favourable and unfavourable results. For each of these extremes, a test for treatment effect in the population (signed ranks test) and confidence interval can be calculated, and the interpretation of them is considered. An approximation to the simulation can be used. An example is given of a half-face study assessing a treatment for crow's feet wrinkles where it was found that measurement error does not affect the interpretation of the study results.

34. A combined penalty approach for classification and biomarker selection

Eleni Vradi (Bayer AG)

The growing role of targeted medicine has led to an increased focus on the development of actionable biomarkers. Current penalized selection methods that are used to identify biomarker panels for classification in high dimensional data, however, often result in highly complex panels that need careful pruning for practical use. In the framework of regularization methods a penalty that is a weighted sum of the and norm has been proposed to account for the complexity of the resulting model. In practice, the limitation of this penalty is that the objective function is non-convex, non-smooth, the optimization is computationally intensive and the application to high-dimensional settings is challenging. In this paper we propose a stepwise forward variable selection method which combines the with or norms. The penalized likelihood criterion that is used in the stepwise selection procedure results in more parsimonious models, keeping only the most relevant features. Simulation results and a real application show that our approach exhibits a comparable performance with common selection methods with respect to the prediction performance whilst minimizing the number of variables in the selected model resulting in a more parsimonious model as desired.

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35. Analysis of direct and indirect pathways via a categorical mediator

Annie Burden (Quanticate)

Inflammatory rheumatic diseases, such as ankylosing spondylitis (AS), are a major cause of work disability. Despite clinical progress in inflammation control and associated improvements in outcomes, work disability remains an issue for AS patients; and other underlying causes, such as fatigue, are postulated. Data from an observational study which followed a large cohort of AS patients in routine clinical practice for 12 months were used to investigate the longitudinal relationship between fatigue and work disability; and in particular, to investigate the hypothesis that the effect of fatigue on work productivity loss is mediated by anxiety/depression. Specifically, an analysis of all direct and indirect pathways from fatigue at baseline to work productivity loss at 6 and 12 months was carried out. Mediation methods described in the literature focus on the mediator as a continuous variable; and the use of linear regression models to estimate indirect effects via continuous mediators (employing bootstrapping techniques to calculate CIs) is well documented. However, for a categorical mediator such as anxiety/depression (patient-reported as none/some/extreme), approximate methods had to be developed using generalised linear models and, again, bootstrapping to calculate CIs.Using this approach, a complete picture of the direct and indirect pathways from fatigue at baseline to work productivity loss at 6 and 12 months could be mapped; providing insight into the mechanism by which fatigue affects work productivity loss. The utility and limitations of the methodology are discussed in relation to a substantive interpretation of the results; as well as the potential for further development.

36. Realising Personalised Healthcare: Statistical Considerations in Development of Companion Diagnostics

Rachel Lawrance (RL Biostatistics Ltd)

In order to realise the goals of personalised healthcare approaches, new medicines have to be prescribed to specific groups of patients who are commonly identified by means of a diagnostic test. In the USA, a diagnostic test is considered as a medical device and is known as a companion diagnostic; a specific companion diagnostic must be approved by the FDA together with a corresponding drug. In 2016, 25% of NMEs approved by the FDA included a companion diagnostic. The need for a companion diagnostic should be identified early in the drug development process and co-development of the drug and companion diagnostic test should be well planned. This poster reviews some of the key statistical challenges posed for a companion diagnostic development and submission to regulatory authorities, particularly focussing on statistical methods and considerations required to demonstrate clinical efficacy in the scenario where a companion diagnostic bridging study approach is required.

37. Does SUMMIT have the X-factor?

Julie Anderson (GSK)

The SUMMIT study (Lancet 2016; 387:1817–26) assessed the effect of inhaled treatment with a combined corticosteroid (ICS) and long-acting β agonist (LABA) on endpoints including overall survival, time to a composite cardiovascular event, decline in Forced Expiratory Volume in 1s (FEV1) and time to first COPD exacerbation, in patients with moderate COPD and heightened cardiovascular risk. The primary comparisons were of this combination arm with a placebo arm, but because regulatory guidelines on combination products require each component contribute to the effect of a combination therapy, ICS and LABA monotherapy treatment arms were also included. In the main CSR analyses treatment arms were compared in pairs. In this poster we present factorial analyses of these endpoints to assess whether the ICS and LABA components interact and to obtain overall estimates of the contribution of each component. The factorial analyses enabled a structured approach to confirm the informal conclusions drawn from the pairwise comparisons. Whilst the four treatment arm model and the factorial models are just different parameterisations, the primary comparison of ICS/LABA vs. placebo is much easier to implement and communicate in the former and the overall component effects and interaction much easier to implement and communicate in the latter. A dual approach to factorial designs where the primary interest is in the combination arm may facilitate communication of results with clinical colleagues.

38. Exploring the impact of censoring on Maximum Likelihood Estimation and Hazard ratios with the use of time to event data

Charlotte Eden (Quintiles)

Time to event data is known to follow distinct data patterns and by use of appropriate analysis methods, insight to potential bias and changes between groups may be seen if present by exploring differing sample sizes. Through the use of simulation, research aims to explore the impact on statistical estimates describing time to the occurrence of an event in the presence of censoring.

Estimates produced show the most probable value expected and a quantifiable value for differences between two groups assigned as arbitrary treatment in seeing an event occur. Conclusions look to investigate the location of estimates, as well as gaining an understanding for the validity of conclusions across groups. Findings show that censoring rates and sample sizes introduce a level of bias to estimation. As an overall summary, estimates are deemed as most accurate as censoring rates are lower and sample size increased, due to the amount of variation in the data being reduced. As mirrored by the proportions of samples that contain the expected maximum likelihood estimates and hazard ratios for both a sample against expected values based on non-censoring and group averages. Suggestions for future research that could be performed in order to assess the impact in bias of the estimates including, adjustments for assumptions based on the sampled data, making use of alternative measures of summary statistics and expanding the number simulation repeats may grow conclusions to the area of study.

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39. An evaluation of statistical methods for predicting timelines for reaching target number of events in clinical trials with time-to-event endpoints

Hans-Joachim Helms (Roche)

In clinical trials with time-to-event outcomes, interim or final analyses are often conducted once a pre-defined target number of events have been reached. Early estimates of the timing of such event-driven analyses are typically based on protocol assumptions and as such unconditional on the actual trial data. As events accumulate during the study a blinded re-evaluation of this prediction is recommended conditional on trial data to obtain a more accurate prediction. Different statistical methods have been proposed in the literature for making such predictions, including parametric approaches assuming smooth underlying survival functions, nonparametric approaches and hybrid methods applying a non-parametric model where data are available, complemented with a parametric tail for regions where no data are yet available. Factors such as study design and ratio of number of events in relation to sample size can imp act the model estimates derived from the various statistical methods, thereby making the choice of the optimal prediction method for a particular study a key decision which can influence the reliability of the predictions. We report results obtained from a systematic comparison of the different methods via simulation studies. The point estimates of the predicted analysis times and number of events, along with their variability as measured by a confidence interval, are investigated under varying study scenarios and findings are discussed.

40. Q-TWiST in Oncology – Is there a standard statistical approach?

Sarah Simpson (Lancaster University)

Aims: Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) combines survival, progression-free survival and quality of life (QoL) endpoints in one analysis. This may be useful where there are differences between treatments with respect to time with side effects and time to progression as both quality and quantity of life are accounted for. Our aim was to review implementation of Q-TWiST analyses in oncology and identify if there is a standard statistical approach to the analysis.

Methods: A literature review was conducted to identify oncology studies using Q-TWiST analysis. Methods were reviewed to establish if there was consistency when defining health states and corresponding utilities. The health states were defined as periods where patients experience toxicity (TOX), no symptoms or toxicity (TWiST), and the period after relapse (REL).

Results: REL was consistently defined as the time from progression to death. There are different approaches to defining TOX and the health state utilities to weight for quality of time spent in a health state. Toxicity may be defined using Grade 3/4 adverse events or sometimes covers the whole treatment period. Utilities are either directly measured or threshold analyses are used to test robustness of the choice of weighting. The methodology for Q-TWiST is often unclear, not reported or lacks justification.

Conclusions: Q-TWiST analysis is useful for weighing up an increase in survival with detrimental effects on quality of life. However, there is a clear need to standardise the statistical approach to ensure results are comparable across different treatments and studies.

41. An adaptive design for Phase II cross-over dose finding trials using Bayesian model averaging

Sarah Simpson (Lancaster University)

Finding the right dose of a novel treatment is one of the most important tasks in early drug development. Often there is uncertainty about the form of the relationship between dose and response. We present a novel adaptive approach for Phase II dose-finding trials that use a cross-over structure. The approach considers multiple dose-response models that are combined using Bayesian model averaging, for estimation of the minimum effective dose (MED). Prior model parameters are found by eliciting pseudo data from experts based on quantiles of the response distribution on placebo and a number of active doses. An optimisation routine is undertaken to search over combinations of prior model parameters and probabilities. The optimisation minimises the absolute difference between the elicited quantiles and quantiles estimated by the marginal distribution of non-central t-distributions for each model multiplied by its prior probability. An adaptive procedure is then implemented across cohorts of patients to identify which doses should be allocated in order to maximise the amount of information about the dose - response curve around the MED. This involves minimising the variance of log(MED), weighted by model probabilities, by searching over combinations of the available active doses in the trial and placebo. Doses are then allocated to patients using a Williams square design to minimise period effects during cross-over of treatments. Model probabilities will be estimated for use in interim analyses and updated after each cohort. Simulation studies will be presented to show evidence of advantages over non-adaptive procedures and those using single assumed dose-response models.

42. Sample size calculation in the presence of non-proportional hazards

Arijit Sinha (Roche)

Sample size calculation for time-to-event endpoint in a two-arm study is typically carried out assuming hazards are proportional. However, in many instances the survival curves separate out later during the study thus suggesting non-proportionality of hazards. While for proportional hazards (PH) standard software can be used for sample size determination, for non-PH standard methodology is still lacking. We explore few different approaches using software and simulation in the context of a specific case study. Method of cure fractions has been used for simulations and future extension to multi-arm clinical trials in the presence of stratification factors has been investigated. Development of R shiny app is currently under way.

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43. Using Power Contours to Assess the Sensitivity of Clinical Trial Design Assumptions

Richard Zink (JMP Life Sciences / SAS Institute)

Sample size calculations are an important part of the design of any clinical trial. These calculations ensure a sufficient number of patients to detect a clinically-meaningful difference between two treatments with high probability. Perhaps less-often discussed, the sample size exercise is important so that resources are not wasted studying too many observations to test a particular hypothesis. Since patients may be randomized to doses of a novel treatment with a limited safety profile, or a placebo which provides no therapeutic benefit, sample size calculations in clinical trials come with an ethical burden not experienced in many subject-matter areas. Unlike many textbooks that perform a single calculation to design an experiment, the sample size of a clinical trial should be determined using as much data as is available, over a range of assumptions, and with input from clinical colleagues. Graphical techniques are often utilized to summarize power and sample size calculations. We propose the use of contour plots to better assess, report and communicate the sensitivity of clinical trial design assumptions.

44. Rethinking the Clinically-Based Thresholds of TransCelerate BioPharma for Risk-Based Monitoring

Richard Zink (JMP Life Sciences / SAS Institute)

The quality of data from clinical trials has received a great deal of attention in recent years. Of central importance is the need to protect the well-being of study participants and maintain the integrity of final analysis results. However, traditional approaches to assess data quality have come under increased scrutiny as providing little benefit for the substantial cost. Numerous regulatory guidance documents and industry position papers have described risk-based approaches to identify quality and safety issues. In particular, the position paper of TransCelerate BioPharma recommends defining risk-thresholds to assess safety and quality risks based on past clinical experience. This exercise can be extremely time-consuming, and the resulting thresholds may only be relevant to a particular therapeutic area, patient or clinical site population. In addition, pre-defined thresholds cannot account for risks that may change over the course of a clinical trial, and often do not consider varying patient exposure. In this talk, we appropriate rules commonly utilized for funnel plots to define a traffic-light system for risk indicators based on statistical criteria that considers the duration of patient follow-up. Further, we describe how these methods can be adapted to assess changing risk over time. Finally, we illustrate numerous graphical approaches to summarize and communicate risk, and discuss hybrid clinical-statistical approaches to allow for the assessment of risk at sites with low patient enrolment.

45. Using Big Data to Facilitate Clinical Trial Enrolment Planning

Steve Jones (Covance)

According to a paper published in Applied Clinical Trials in 2015, 19% of studies, closed or terminated in 2011, either failed to meet accrual goals (85% of expected enrolment) or were terminated due to insufficient accrual. Finding this poster presents applications of statistical methods in the field of Big Data to help identify new sources of patients and investigators and to help evaluate the impact of inclusion/exclusion criteria on enrolment rates (screen failure rate) with the aim to evaluate up-front the risks of slow enrolment versus the cost of increased site numbers and/or modification of the trial design..

46. Big data meets Pharma

Orlando Doehring (PHASTAR)

In this work we present a tutorial introduction to show how SAS can be leveraged for large datasets in the pharmaceutical sector: Big data plays an increasingly important role within drug compound discovery, genomic data analysis in clinical trials and real-time streaming data from wearable devices or sensors which monitor patients' health and treatment compliance. SAS adopted Hadoop as highly scalable data platform for data warehouse operations, descriptive statistics and statistical analysis with a bias towards machine learning approaches. However, Hadoop' MapReduce framework is slow and batch-oriented which is not very suitable for iterative, multi-step parallel algorithms with a focus on in-memory computations. To address these limitations SAS added layers for in-memory computation, interactive data queries using a SQL variant, support for streaming analytics and predictive models implemented in SAS Visual Statistics/Analytics. In the data science sector, the similar open-source Apache Spark project with its machine learning library MLlib is commonly used. Both Visual Statistics and MLlib have implementations for linear/logistic regression, decision-tree based classifiers, and clustering. Furthermore, SAS focusses on group-by processing and GLMs while MLlib has methods for feature extraction, dimensionality reduction, SVM classifiers, matrix completion and basic hypothesis tests. At the moment the SAS Hadoop implementation is a good selection for data management and dataset derivations which often can be parallelized. However, currently there is lack of procedures typically in pharmaceutical statistics, such as mixed effect models for repeated measurements analysis or survival analysis models.

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47. Bayesian modelling of the placebo response in neuropathic pain

Samuel Branders (Tools4Patient sa.)

In analgesia randomized clinical trials (RCTs), the magnitude and the variability of the placebo response have a negative influence when testing the statistically significant superiority of active compounds compared to placebo. Furthermore, the magnitude of this effect has tended to increase over time, including in peripheral neuropathic pain (PNP) trials. The main objective of this study was to investigate parameters influencing the placebo response as a way to control this major confounding factor.

Eighty-seven PNP patients were enrolled and blindly given a placebo during 4 weeks. The placebo response was estimated as the difference in pain between baseline and end of the treatment. In addition, patients filled a psychological questionnaire at baseline assessing several components of their personality. We modelled the placebo response from patient's characteristics using a Bayesian machine learning approach: Gaussian processes with a linear kernel. The covariates used in the model were selected using a multivariate recursive feature elimination (RFE). The advantage of this Bayesian modelling is to predict the placebo response and to give confidence intervals on the predictions. The predictive performances of this model were estimated in a repeated random sub-sampling scheme (or Monte Carlo cross-validation). The model explained almost 30% of the variance in new patients (p-value<0.001). Using the model predictions as a covariate could thus reduce the placebo variance by 30% in subsequent PNP studies. This reduction of variance could in turns lead to an increased effect size and study power. Such a tool to characterize and predict this important source of variance would thus be of great value in analgesia randomized clinical trials.

48. Performing Statistical Analysis on "Big" Project Dataset to Mine Associations and Identify Data Issues on an Ongoing Basis

Shafi Chowdhury (Shafi Consultancy Limited)

The use of standard SDTM structured data has given us the opportunity to generate one "BIG" dataset by merging different SDTM datasets together. This can merge all related data together by defining the key identifying variables within those datasets. The advantage of doing this is that we are then in a position to see how all the data relate to each other. Statistical analysis can be performed automatically to check associations of all types of data based on age, sex, race, country and all other covariates specified within a project. Any associations can be highlighted and potential data quality or trends in the data can be explored on an ongoing basis prior to database lock. Graphical tools can be used to see how values are changing over time, and if there are unexpected events in the target population. When the "big" datasets from multiple studies are combined, then trends can be analysed, and different endpoints or outcomes explored in a manner that is too time consuming in the current environment. Recruitment rates, inclusion exclusion failures, randomization, protocol violations, early terminations and lost to follow up, serious adverse events, prohibited medications, outcomes and endpoint issues can all be analysed on an ongoing basis to see if there are any relationships that should be explored. Any unexpected results or findings can then be investigated and actions can be taken if required to help raise the quality of the data as soon as any issues are found.

49. Improving regional effect estimation with single-arm bridging trials

Jixian Wang (Celgene)

Estimation of regional treatment effects becomes increasingly important as regional health authorities and payers are concerned about benefit-risk and cost-effectiveness of medical products in their specific population, which may not have sufficient representation in global registration trials. Single arm bridging trials of small sample size are often used to assess treatment effects in specific regions such as Japan or China. However, due to the lack of a control group, treatment effects compared with placebo cannot be estimated based on the study alone, and a direct comparison to the control group in global trials is likely confounded due to differences in the patient populations of these studies. We propose using the propensity score (PS) to assess similarity between global and bridging trials to determine if results from both trials are comparable. When they are not comparable, we propose a novel approach using the covariate balancing PS to adjust for confounding factors in the comparison. Although the inverse probability weighting (IPW) approach based on the PS can also be used for this purpose, it is sensitive to misspecification of the PS model. The covariate balancing PS based IPW can balance confounders even when the PS model is mis-specified, hence is more robust than the PS based IPW. To examine the performance of the proposed approaches, we conducted a small simulation study and the results showed good performance of the approach. An example is used to illustrate implementation of the approach and practical considerations.

50. Contributing towards Increasing Statistics Capability in sub-Saharan Africa

Lindsay Kendall (GSK)

The demand for qualified experienced statisticians in sub-Saharan Africa is very high, growing, and outnumbers the supply. In response GSK has committed to help increase statistical capabilities on the continent as part of the Africa Non-Communicable Disease (NCD) Open Lab. The Africa NCD Open Lab was established in 2014 as part of a series of GSK's strategic investments to provide long term support for scientific research in the field of NCDs in sub-Saharan Africa. The goal is to work in partnership with funders, researchers and academic groups to share expertise and resources to increase the scientific understanding behind the unique attributes of NCDs in the African population. Five projects have been selected to receive GSK funding as part of the first call for proposals (launched Nov-14), several projects have been chosen to progress as part of a joint call for proposals between GSK, MRC UK and MRC South Africa (announced

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Sep-15) and a third call for proposals, targeting early career researchers, launched in Nov-16.

- GSK statisticians are currently providing statistical support for all GSK funded and co-funded Open Lab projects. Support ranges from consulting with the project teams on design issues, sample size calculations, protocol development and analysis considerations.

- In 2017 GSK plans to host a one week summer school for African statisticians at GSK's R&D facilities in the UK. The aim is to roll out focused training sessions and to provide an opportunity for networking.

- Other initiatives are also under development.

51. Empowering global team success

Sally Anderton (PPD)

The role of the statistician in the pharmaceutical and CRO industry has changed substantially over recent years and working on global teams is part of the statistician's and programmer's roles more than ever before. Understanding and effectively dealing with our differences is crucial to our success... while we have come a long way on many topics to have common understandings some location-specific practices still exist and can be very different from location to location. When we establish or expand teams across office locations, if we are not proactive in understanding these differences, during dense periods of activity when the pressure is upon us to deliver, these differences across sites combined with time-zone differences could have the potential to impede our success. PPD has therefore made cultural and global working training a priority, giving teams the knowledge and skills they need to make their global teams a success.

52. MSc in Statistics – is it the be-all and end-all to a career as a pharmaceutical statistician?

Marsha Kabeleva (Quanticate)

The vast majority of pharmaceutical companies and CROs ask for an MSc in Statistics (or Medical Statistics) when hiring statisticians, claiming these degrees in particular provide adequate preparation and the necessary hands-on experience to work in the industry. However – how strict is this rule across different companies, and is it even necessary? Can similar qualification such as an MMath or PGDip be equivalent and provide the required statistical training for a career in industry? As well as drawing on my own experience with job applications, attending careers fairs and working as a junior statistician at Quanticate while possessing an MMath, I will talk about the experiences of other statisticians with similar qualifications, as well as the opinions of recruiters. Results will be presented from a survey of various senior statisticians and industry heads, about their perceptions of alternative qualifications and which specific aspects they consider important in a course. Finally I will present and discuss some examples of statistical/mathematical courses in UK universities, to demonstrate how content and projects can vary widely, and how an MMath in some universities can cover the same topics and applications as an MSc in others.

53. CALC 2016/2017

Katie Thorn & Jemma Greenin (Eli Lilly)

The PSI Careers and Academic Liaison Committee (CALC) aim to provide and deliver information about working in the pharmaceutical industry to students of all ages. The committee is formed of thirteen industry volunteers working together across companies. In the past year, CALC has taken on multiple new endeavours as well as maintaining to grow existing events, such as the PSI Careers Event. This poster highlights CALC's achievements of the past 12 months.

2017 PSI Conference

For general conference queries please contact the conference organisers at the following address:

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