Cluster stability for more robust classification in Triple-Negative Breast Cancer

Martina Sundqvist, Leanne de Koning, Guillem Rigaill, Thierry Dubois, Julien Chiquet

KEYPOINTS

- A new classification of Triple Negative Breast Cancer based on **proteomic data**.
- Cluster stability was measured by **resampling** methods.
- The classification is already **validated** in a secondary dataset.
- 18 proteins were shown to be critical for this classification **encouraging further clinical investigation**.

AgroParisTech
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#1

Predictive Performance of Bayesian and Population Pharmacokinetic (POP PK) Analysis Approaches for Prediction of Exposure During First Time in Human (FTiH) Dose Escalation

Carlton A, Tenero D, Wang Y, Goyal N

Poster No. **2**

Intro	Randomised, dose-escalation study including single dosing and repeat dosing phases. Exposures limited to pre-defined levels based on area under the curve and maximum concentration. Bayesian power model and population pharmacokinetic mixed effects modelling were used to predict drug concentrations at other dosing regimens.
Results	Both methods underestimated the probability of an individual exceeding the exposure limits but the POP PK approach provided better predictions overall compared to the Bayesian approach.
Conclusions	Given the current data, the POP PK approach would be the preferred approach for a future study, of a comparable size, requiring predictive exposure for dose escalation.

3. Using latent class mixed model for bioequivalence test in unknown heterogeneous population

Eunjung Song [1], Bo-Hyung Kim [2], Sungjeong Lee [1], Woojoo Lee [1]

1) Department of Statistics, INHA University 2) Department of Clinical Pharmacology and Therapeutics, Kyung Hee University College of Medicine and Hospital

Objective

- One of key assumptions for the bioequivalence testing procedure is the homogeneity of population.
- However, the pharmacokinetic data (AUC or Cmax) often show heterogeneous properties in terms of mean level, intra(within) variance or inter(between) variance.
- As an alternative solution, we propose to perform the bioequivalence test with the latent class mixed model (LCMM) to deal with the situation where the class label of individuals in the heterogeneous population are unknown.

LCMM for the bioequivalence test

$i = 1, ..., N$: subject, $j = 1, ..., n_i$: repeated observation

$\eta_i \sim N(0, \omega^2), \quad \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$

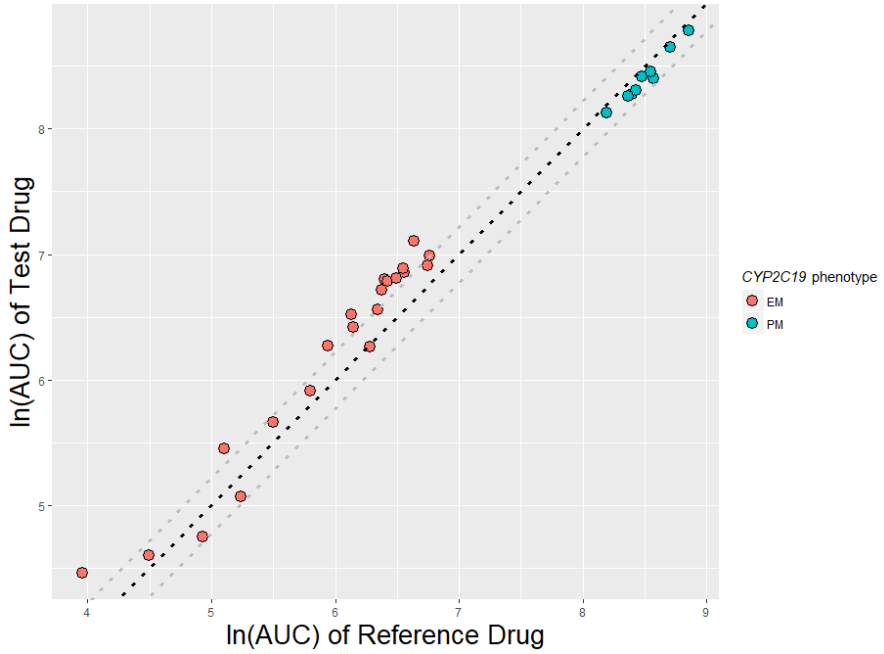
y_{ij}: ln(AUC) or ln(Cmax)

PRD_{ij} : Period, SEQ_{ij} : Sequence, TRT_{ij} : Treatment, Z_i : latent group

Given Z_i, $y_{ij} = \beta_0 + \beta_1 PRD_{ij} + \beta_2 SEQ_{ij} + \beta_3 TRT_{ij} + \beta_4 Z_i + \beta_5 Z_i\, TRT_{ij} + \eta_i + \varepsilon_{ij}$

$$y_{ij}\Big|_{Z_i=0} = \beta_0 + \beta_1 PRD_{ij} + \beta_2 SEQ_{ij} + \beta_3 TRT_{ij} + \eta_i + \varepsilon_{ij}$$

$$y_{ij}\Big|_{Z_i=1} = (\beta_0 + \beta_4) + \beta_1 PRD_{ij} + \beta_2 SEQ_{ij} + (\beta_3 + \beta_5) TRT_{ij} + \eta_i + \varepsilon_{ij}$$



Exploring re-randomisation tests in an equivalence trial

Holly Prescott, Marsha Kabeleva and Niccolo' Bassani

Poster #4

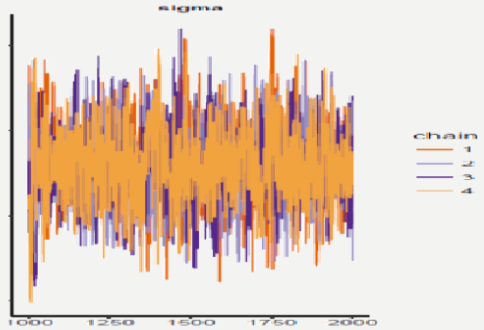
Quanticate
The Clinical Data Experts

- Re-randomisation tests, which imply re-shuffling of treatment labels between patients, are used in many settings to confirm 'conventional' test results.
- EMA/CHMP 'Guideline on adjustment for baseline covariates in clinical trials' refers to them as a viable approach to maintain type I error control in certain scenarios (e.g. dynamic randomisation)
- This holds fine for superiority studies, but what about equivalence studies?
- Based on a real request from the EMA for a biosimilar development, some caveats and considerations will be discussed, supported by simulated data.

5. A Bayesian approach to nonlinear mixed effect models for pop PK/PD data using Stan

Abeera Mohammad

- How to implement models using STAN
- Nonlinear mixed effects models for pharmacokinetic and pharmacodynamics data analysis
- Hamiltonian Monte Carlo



Poster #6:
How to predict a daily concentration for exposure-response analyses when no population PK model is available?

- PK sampling is usually limited to fully support exposure-response analyses (especially in pediatrics)
- Population PK model is the state-of-the-art to predict daily exposure but is not always available
- For drugs with linear PK, we propose the following method.
- Provide PK predictions using basic PK equations and superposition principle to link safety and efficacy to exposure

Authors: Sébastien Lorenzo, Kai Grosch

THE USE OF BAYESIAN METHODS IN EARLY CLINICAL STUDY DESIGN

Susie Collins, Early Clinical Development, Pfizer, Cambridge, UK

- In early clinical research it is important to use all of the information available when designing our early-phase clinical studies. Bayesian methodology is widely employed within Pfizer to formally incorporate historical data in order to run smaller, cheaper, and more ethical studies
- Techniques for incorporating historical data will be discussed, including the use of elicitation to set an informative prior for the between study variance component in cases where there are few historical studies
- Two examples will be presented where Bayesian methods have been employed for the design of an Alzheimer's psychosis study
    1. Combining estimates of variability across historical studies to provide an estimate of variability for input into sample sizing calculations for the future study
    2. Combining placebo responses from the same historical studies into a placebo response prior which can then be incorporated into the statistical analysis of the future study, reducing the number of patients required in the placebo arm
- Using this approach, the planned Alzheimer's study sample size was reduced by 7 subjects (9%), which, although seemingly small, would result in a substantial time (~1-2 months) and cost (~$0.5M) saving in such a hard to recruit early clinical trial

Innovative Approach for Early Phase Clinical Trials – A Case Study

Reetabrata Bhattacharyya

Poster Number: 8

- Bayesian Logistic Regression Model (BLRM):
  A popular method in dose escalation clinical trials
- SAS®, the commonly used software in the industry otherwise, is not generally used for BLRM
- An attempt to develop a user friendly code in SAS® with a real life scenario

Cytel

An application of Bayesian multivariate analysis to an Experimental Medicine clinical trial

Experimental Medicine studies

– Carefully selected population

– Large number of biomarker endpoints, rarely validated, to **understand** the effect of drug on disease

– However, they must make **decisions** about progression

The role of the statistician

– Working with the team to define decision making biomarkers and rules

– Quantifying the properties of decision making

Multivariate Bayesian model

– Natural fit for correlated data

– Useful statements about the posterior probabilities of both individual and joint success across biomarkers

– Estimates correlation between endpoints

– Can use data from external sources to support analysis

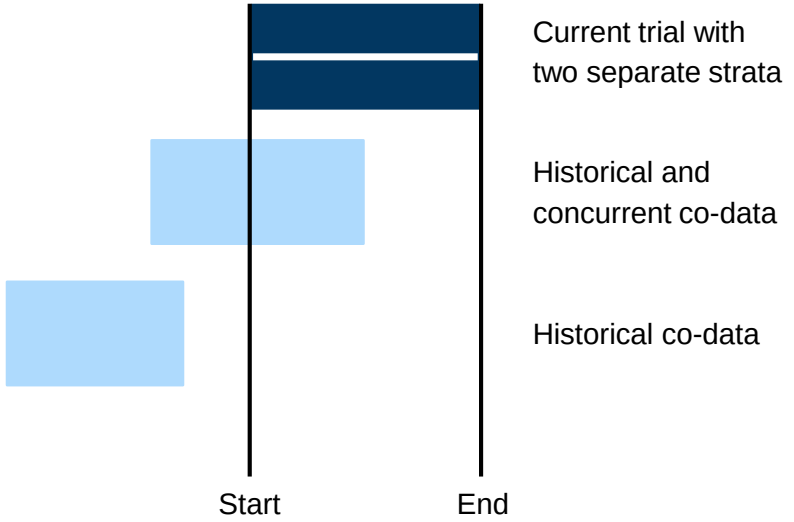
Ken Edwards, poster 9

Poster 12 An Application of the Meta-Analytic-Combined Method in a Phase I Oncology Dose escalation Trial

Tiina Kirsilä[1], Niladri Roy Chowdhury[2], Juan Gonzalez-Maffe[1], Serena Liao[3]

[1]Novartis AG, Basel, Switzerland, [2]Novartis Pharmaceuticals Corporation, East Hanover USA, [3]Novartis Institutes for Biomedical Research, Cambridge USA

- Meta-analytic-combined method allows for simple inclusion of co-data in the dose/toxicity model
  - co-data may come from historical trials, concurrent trials or different strata within the same trial
- Optimises understanding of the dose/toxicity relationship based on all relevant information available



Reference: Neuenschwander B, Roychoudhury S & Schmidli H. On the Use of Co-Data in Clinical Trials, Statistics in Biopharmaceutical Research (2016)

NOVARTIS

Joint Modelling of Efficacy and Toxicity in Dose Escalation Phase I studies

Mounir Aout, PhD

- A method that uses modeling of both toxicity and efficacy to further guide the estimation of the RDs by finding an optimal dose or range of doses that maximizes the efficacy while controlling safety will be presented

- Two models to assess dose-toxicity and dose-efficacy relationships will be presented and the joint distribution of efficacy and toxicity will be estimated using global cross-ratio method

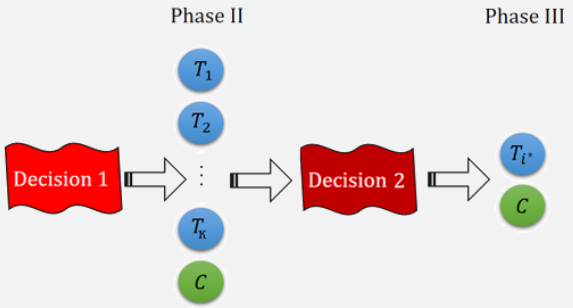
- The operating characteristics of the models using several scenarios of dose-response and dose-toxicity shapes will be provided

- The work presented here has been accepted for publication in OJS journal (https://www.scirp.org/journal/ojs)

Bayesian Decision Theoretic Approaches to Phase II/III Programmes

Robbie Peck, University of Bath, UK

- Treat **Phase II** and **III** as a **programme**.
- Use **Bayesian Decision Theory** to make optimal decisions for the programme.
- **Gain function** specified to represent **Net Present Value**.



Case Study 1: Group Sequential and Adaptive Methods

*What is the value of using **group sequential** and **combination tests** within a Phase II/III programme?*

Case Study 2: Dose Response Modelling

*What is the value of using **dose response models** to model dose response data in a Phase II/III programme?*

Case Study 3: 2 Phase IIIs

*How should one perform Phase III when **2 confirmatory trials** are required when they are fixed sample and **group sequential**?*

Poster 15: Nested Resampling for Projecting Future Outcomes with Application to Decision-Making

What do you do when…

- Multiple decision criteria / endpoints
- Those endpoints are related but unclear how
- Conventional distributional assumptions are most-likely not appropriate …?

Biogen

Facilitating Bayesian Predictive Probability Calculations for Interim Analyses in Early Phase Development at Pfizer

Donal Gorman, ECD Statistics

Figure generated at *https://www.wordclouds.com/*

One-arm trial: comparison of designs with interim analyses based on posterior and predicted probabilities

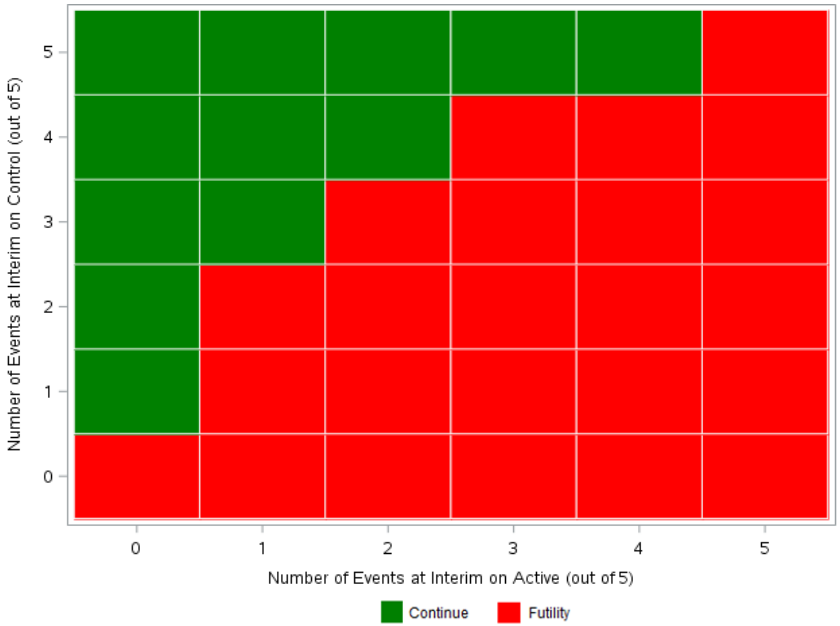
Francesca Michielin - Elias Laurin Meyer

- Have you ever asked yourself what is the difference of using posterior *vs* predicted probabilities in your interim decision making?
- In this poster we look into one-arm trials where decision making is based on a proportion (*e.g. response rate* for oncology) and explore via simulations the operating characteristics of designs which make use of posterior probabilities and predicted probabilities
- If you want to know more about this or simply want to see nice plots come to our poster!

Closed Form Predictive Probability for Interim Decision Making

Valerie Millar and Jane Temple

- When exploring futility analysis, as binary data have a fixed number of outcomes the predictive probability of achieving end of study success can calculated using a closed form approach.
- This is done by taking all possible future combinations of events into consideration, along with the probability of observing those events given the interim data and a non-informative prior (Dmitrienko, 2006).
- From this we can create and present a decision grid for each possible event outcome at the interim.
- This enables potential stopping rules to be presented and discussed with the clinical team in a clear and concise manor.



Reference: Dmitrienko, A., & Wang, M. D. (2006). Bayesian predictive approach to interim monitoring in clinical trials. . *Statistics in Medicine*, 25(13), 2178-2195

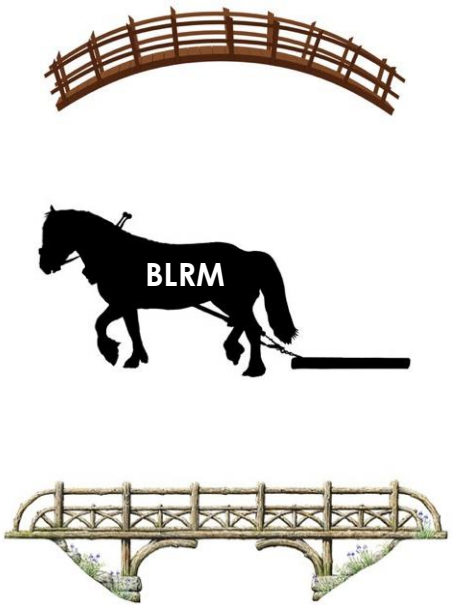
Can Bayesian Logistic Regression Models build bridges to share information?

Other Sources

Pre-Clinical

Epidemiology

Genetics



Randomised Clinical Trials

First-in-man

Efficacy

Safety

Cytel

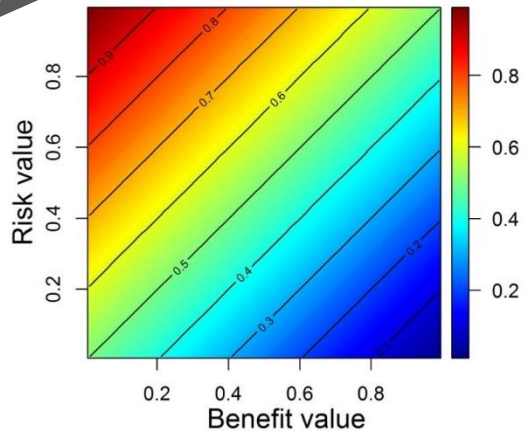
Poster 20

Scale Loss Score (SLoS): a novel measure of drug benefit-risk assessment

Gaelle Saint-Hilary and Pavel Mozgunov

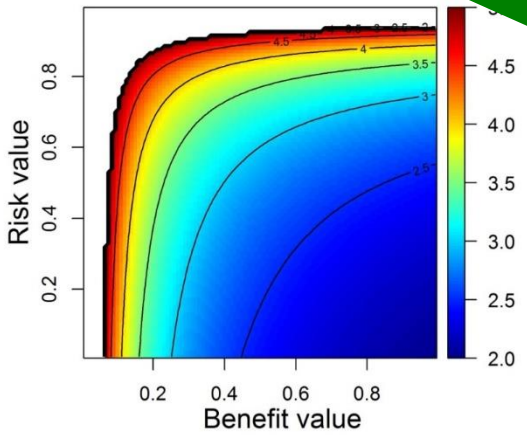
TODAY, USUALLY...

Linear additive MCDA



NEW!

SLoS



- ✗ The benefit-risk trade-off is the same for all values of risk / of benefit
- ✗ Drugs with 0% benefit or 100% risk can be recommended

- ✓ For a given increase in benefit, a larger increase in risk is tolerated if the amount of benefit is small than if it is high
- ✓ Non-effective or extremely unsafe treatments can never be recommended

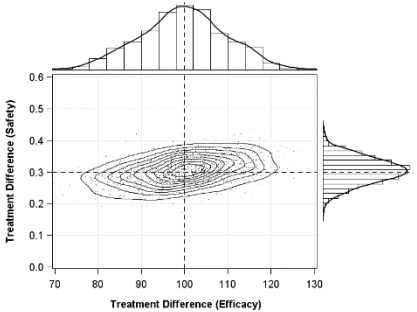
MCDA: MultiCriteria Decision Analysis

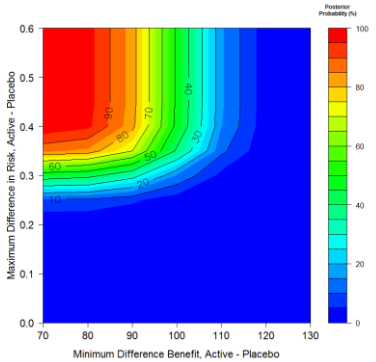
Come to see our poster if you want to know what these rainbows are about!

Bayesian Joint Modelling of Benefit and Risk in Drug Development

Maria Costa (Novartis) & Thomas Drury (GSK)

- Jointly assessing benefit risk in drug development can be challenging, especially where benefits and risks have potential to be associated at the subject level.
- This poster demonstrates two methods for jointly modelling mixed types of BR data allowing for any potential dependency – using Generalized Linear Mixed Models and also Copula modelling.
- Using a framework of Bayesian methods and clinically relevant thresholds, the BR profile for an asset can be constructed using joint posterior probabilities.

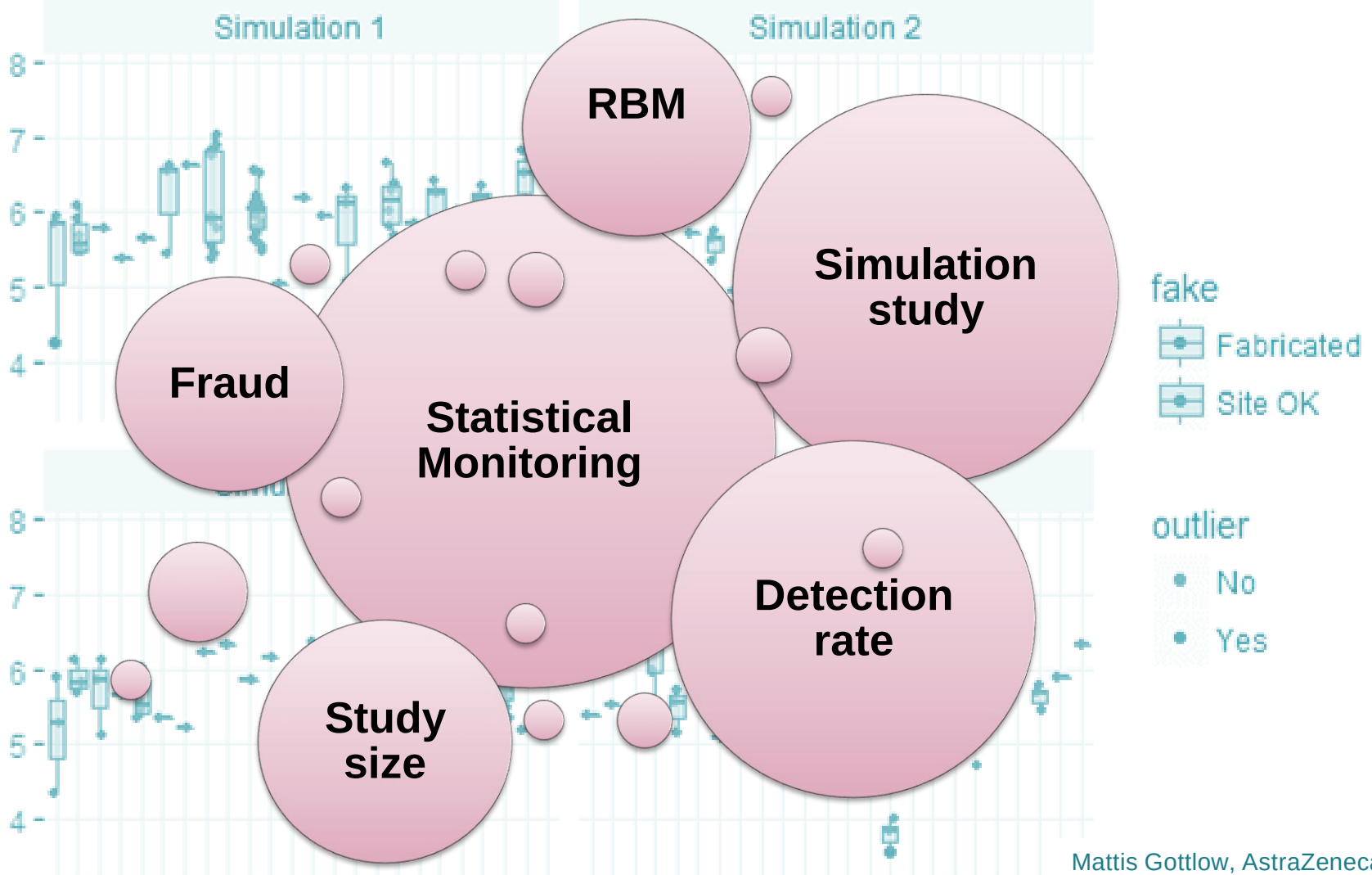




- The information from these type of analyses provide intuitive results that various stakeholders can easily digest.
- The use of the methodology can aid critical decision making demonstrated via simulated examples at various stages of drug development, from proof of concept all the way through to confirmatory trials and submission related integrated analyses.

Costa MJ, Drury T. Bayesian joint modelling of benefit and risk in drug development. *Pharmaceutical Statistics*. 2018;1–16. https://doi.org/10.1002/pst.1852

Detecting data anomalies using limited study data – are centralized statistical monitoring methods useful?



Mattis Gottlow, AstraZeneca

Risk Based Modelling Methods

Santosh Tymms, Laura Grey
Poster #24

Quanticate
The Clinical Data Experts

Problem

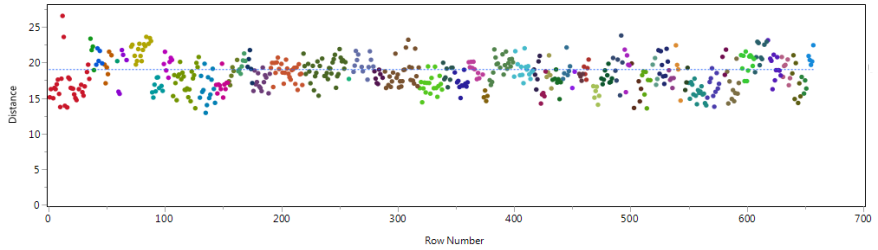
- Vast amount of data - Minimise data errors, maintain patient safety
- Recording, training, potential fraud, professional patients
- Participant, investigator, site, geographic region level.

Investigation

- Onsite Monitoring
- RBM /CM - Formal statistical tests detect anomalies/similarities - Root cause of a problem - Focus OM

Quanticate Solution

- Web-Based Monitoring Platform / Statistical Monitoring Reports
- Anomalous dates, trends in AEs, safety parameter ANOVA and MMRM, digit preference, Mahalanobis distance inliers and outliers



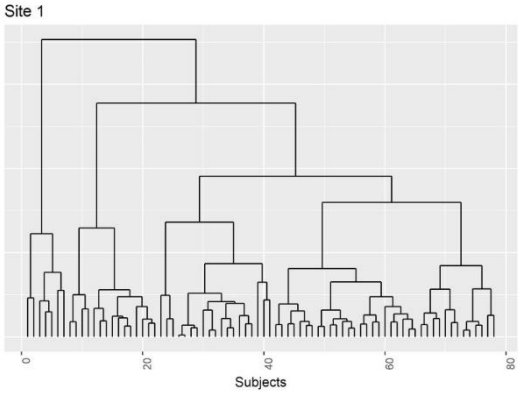
Fraudulent data detection in clinical trial using dynamic clustering

Goal: - Identify problematic sites
- Use dynamic clustering approach
- Improve overall efficiency

Methodology:

- Use variables with unique characteristics/site
- Use Duda & Hart method to identify primary number of clusters per site
- Rectify actual number of clusters using model based clustering
- Check relationship of homogeneous clusters from different sites to identify inequalities
- Repeat the process over the period of data collection

Dendrogram: subject grouping for site 1



Site	1	2	3	4	5	6	7	8	9
No. of Cluster(s)	1	2	3	1	1	1	1	2	4
DH Index	0.741	0.588	0.620	0.794	0.663	0.863	0.696	0.670	0.602

Based on clustering information and somers' D statistics, site 9 has indication of fraudulent data as it belongs to less homogenous group.

Retrospectively Implementing the Estimands Framework for a Large Phase IV Safety Study: Challenges and Considerations

Leanne Hall

- For a study which predates the draft ICH E9 addendum, this work sought to utilise the estimands framework whilst aligning to the protocol and to also consider the approach that may have been taken prior to the release of the draft addendum.

- Several strategies for handling of intercurrent events were considered for the primary endpoint of mortality, including while on treatment, hypothetical and treatment policy.

- A tipping point analysis considering all possible outcomes for missing mortality status was performed, based on simulated data.

Imperial College London

Lessons to learn from the reporting of adverse events (AEs) in randomised controlled trials: a systematic review of published reports in four high impact journals

Rachel Phillips, Lorna Hazell, Odile Sauzet and Victoria Cornelius

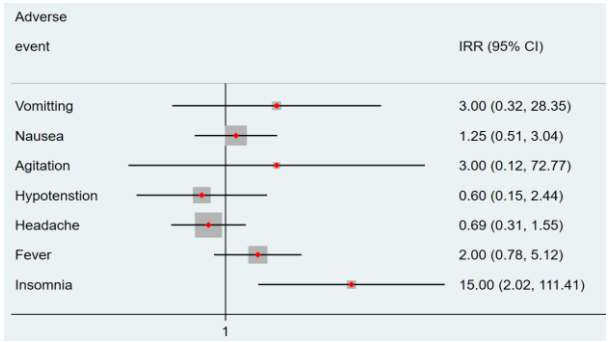
Aim: Review current **best** practice in 4 high impact medical journals.

Key messages

- The review demonstrated that even in best practice the collection, reporting and **analysis** of AE data in clinical trials is sub-optimal.
- Clear area to improve is reducing information loss when analysing at patient level.
- Hypothesis testing is prevalent, we would benefit from better statistical methods being developed.

Adverse event	Intervention		Control		
	n	%	n	%	p-value
Vomitting	3	0.03	1	0.01	0.312
Nausea	10	0.1	8	0.08	0.621
Agitation	1	0.01	0	0	0.316
Hypotenstion	3	0.03	5	0.05	0.471
Headache	9	0.09	13	0.13	0.366
Fever	12	0.12	6	0.06	0.138
Insomnia	15	0.15	1	0.01	<0.001
.....					

Potential alternative.....



Poster 27

Modeling and Simulation in Support of the Development of an Orphan Drug - Dengue as a Case Study

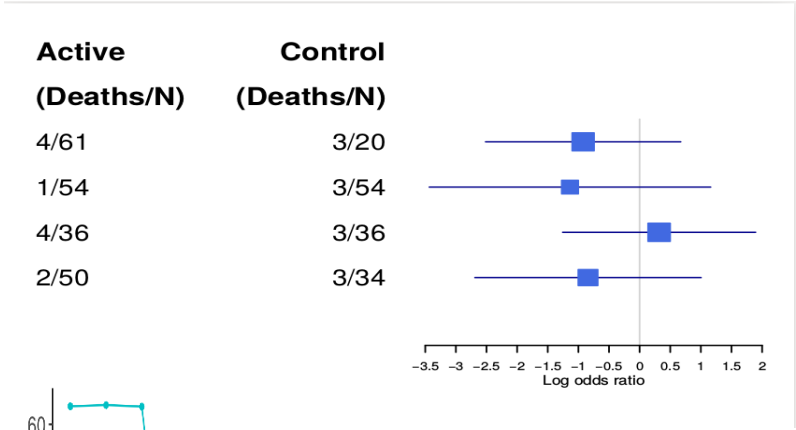
J. Menten, S. Masyn, O. Ackaert, A. Vandebosch, M. Van Loock, G. Herrera-Taracena
Janssen Pharmaceutical Companies of Johnson & Johnson

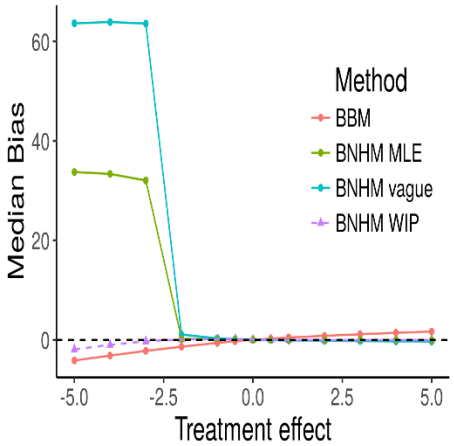
Poster Nr. 28

- Dengue is an *important public health problem*
- *Outbreaks* can be local and time limited
- Understanding outbreaks is critical in *planning clinical trials*
- We prepared and extensive *modeling and simulation package* to support dengue drug development, including:
  1. infectious disease transmission modeling
  2. clinical trial simulation
  3. tempero-spatial and geo-spatial modeling
  4. viral kinetic modeling
  5. epidemiological studies

Meta-analysis of rare events with few studies

- Random effects meta-analysis with few studies
- Further complications by rare events, eg (S) AEs
- Idea: In Bayesian paradigm, weakly informative priors for the treatment effects and the between-trial heterogeneity
- **MetaStan** R package





Burak Kürsad Günhan, Christian Röver, Tim Friede

The use of MICE in Longitudinal Observational Studies

by Tasmin Arnould, Veramed Limited

- Sparse data is a common problem in observational studies
- Current recommended MICE (Multiple Imputation using Chained Equations) approach is to use all future recordings when imputing covariates measured repeatedly

- **Problems:** Varying number of recordings between patients, varying time between visits and a high drop out rate
- This approach proves difficult when visits occur irregularly

Reliability of observational analyses in light of a re-analysis of the DIG trial

Lukas Aguirre Dávila, Kristina Weber, Udo Bavendiek, Johann Bauersachs, Janet Wittes, Salim Yusuf, Armin Koch

Does digoxin affect mortality?

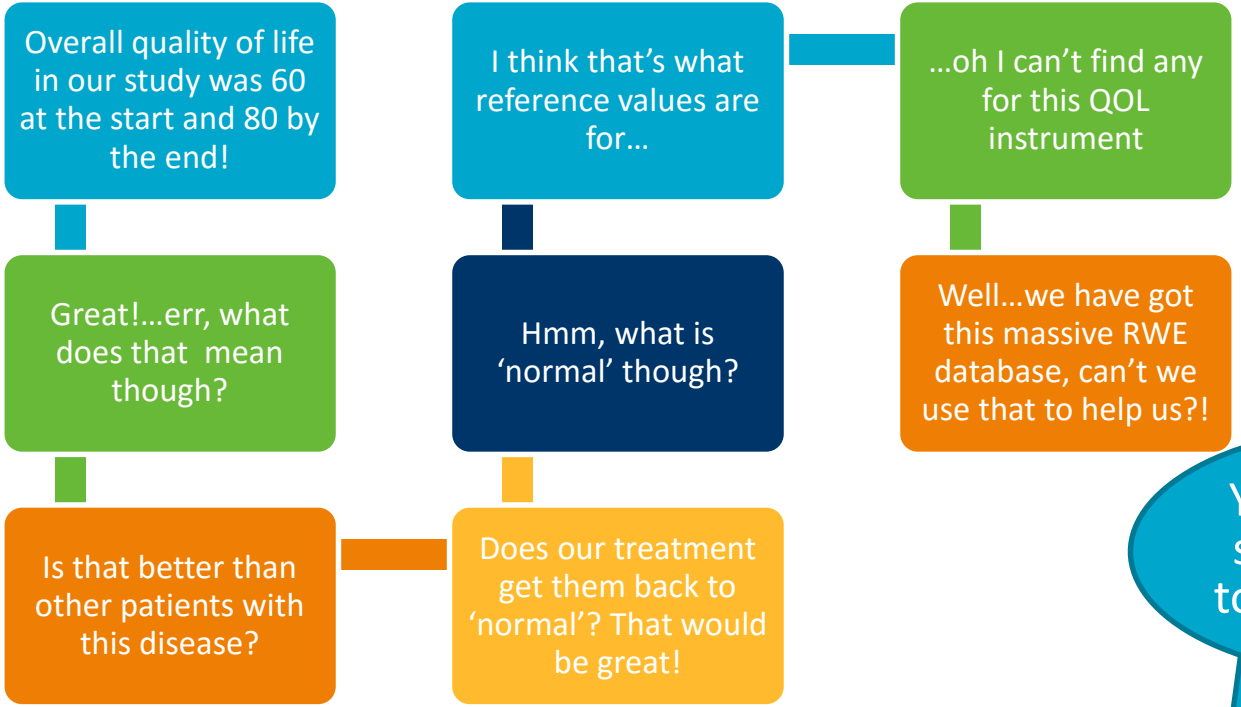
- Randomized trial (DIG): neutral effect (with potential benefits)
- Many observational analyses: potentially harmful effect

We quantify and prove the existence of „prescription bias“ in non-randomized treatment comparisons

Poster number 32

Using real-world data to generate reference values for patient-reported outcome measures

Authors: Kim Cocks[1], Bryan Bennett[1], Elaine Brohan[1], Katherine Byrne[2], Alex Rider[2]
[1]Adelphi Values, Bollington, Manchester, UK; [2]Adelphi Real World, Bollington, Manchester, UK



Adelphi ADELPHI VALUES | Patient-Centered Outcomes | Adelphi ADELPHI REAL WORLD | Leadership in Real World Evidence

Further information:
kim.cocks@adelphivalues.com

Creating a responder definition for patient-reported outcomes: How to select an appropriate cut-off value?

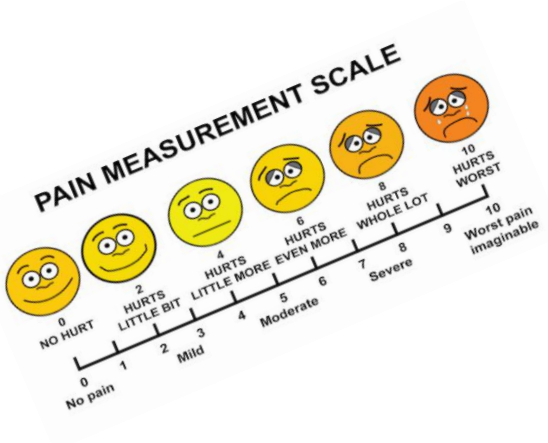
Rhian Jacob (Roche)

Background

What are PROs?
Why are PROs important?
When, **Who** and **How** are PROs used?

Content Validation & Psychometric Evaluation

- **Qualitative:** *content validity*
- **Quantitative:** *construct validity*



Selecting a cut-off

- Distributional Methods
- Anchoring Methods
- CDF Methods

Wearable Devices and Mobile Health – an Opportunity for Innovative Remote Patient Monitoring in Niemann-Pick Type C

S Joksaite; EH Davies; H Cizer

Poster Number: 34

- **Disease.** Niemann-Pick C (NP-C) is a rare inherited neurodegenerative autosomal recessive disorder primarily diagnosed in children. Disease symptoms include frequent falls, ataxia and behavioural problems.
- **Problem.** There is a lack of validated, age-related, disease-specific end points available to monitor gait and ataxia long-term in NP-C.
- **Possible Solution.** Wearable technologies allow daily continuous activity monitoring, and smartphone apps can facilitate Patient Reported Outcome (PRO).
- **Our Objective.** To assess the feasibility of collecting such data for evaluating NP-C disease, and to summarize the wearable device data for clinical context, and application in NP-C and other rare diseases.

Matching-Adjusted Indirect Comparison of Single-Arm Studies using SAS™

William Malbecq, Rachid Massaad, Dave Gelb

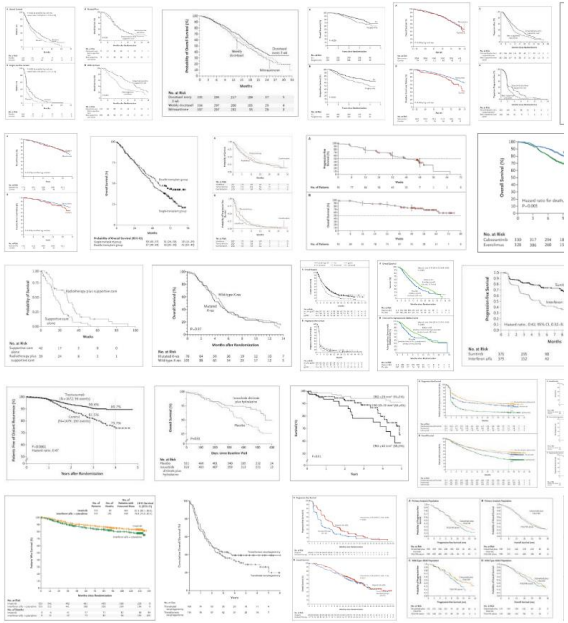
POSTER 35

- For HTA submissions, we applied the MAIC (Matched-Adjusted Indirect Comparison) methodology to compare overall survival of a New Oncology Treatment compared to the Standard of Care.
- Individual Patient Data were available in house for the New Treatment as well as published Aggregate Data for the Standard of Care studies.
- Calculation of the propensity scores was performed through standard SAS™ procedures, without using the Integrated Matrix Language (IML).
- We discuss the results of the naïve treatment comparison and how the adjusted comparison improves the estimate. Patient characteristics, overall survival curves and summary statistics are presented.

MSD

Non-Proportional Hazards in Network Meta-Analysis: Efficient Strategies for Model Building and Analysis

Anna Wiksten, Novartis Pharma AG, Basel, Switzerland and Dr. Sandro Gsteiger, F. Hoffman-La Roche Ltd, Basel, Switzerland



Source: Google images screenshot

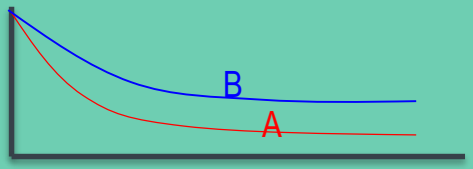
- Objective:
  - Evidence synthesis of non-proportional hazards TTE data from published Kaplan-Meier curves
- Methods:
  - Bayesian and frequentist NMA using a Generalised Linear Models framework
- What was innovative:
  - Expressed a wide range of time-varying hazard ratio models as GLMs to allow efficient model building
- Highlight of the results:
  - Greatly reduced time for computing and model building
  - Combining several approaches and taking the best from all
    - Different NMA methods
    - Bayesian and frequentist methods

Cox proportional hazards assumption in the light of novel immunotherapies: a case study of network meta-analysis with time-to-event

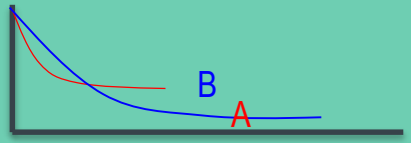
Sory Traore and William Malbecq, BARDS HTA Statistics, MSD

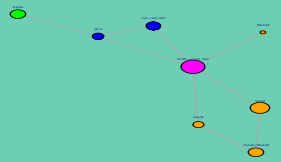
Bayesian NMA/MTC for time-to-event outcomes in *winBUGS*

1. 'Traditional' approaches based on relative effects: Hazard-ratios under proportional hazard assumption



2. Non-proportional hazards (NPH) approach based on Fractional polynomials





3. Case study

4. Conclusion: The results suggest that both unidimensional parameter as the HR under PH and more sophisticated time-dependent HR derived from parameter estimates are complementary for a correct interpretation

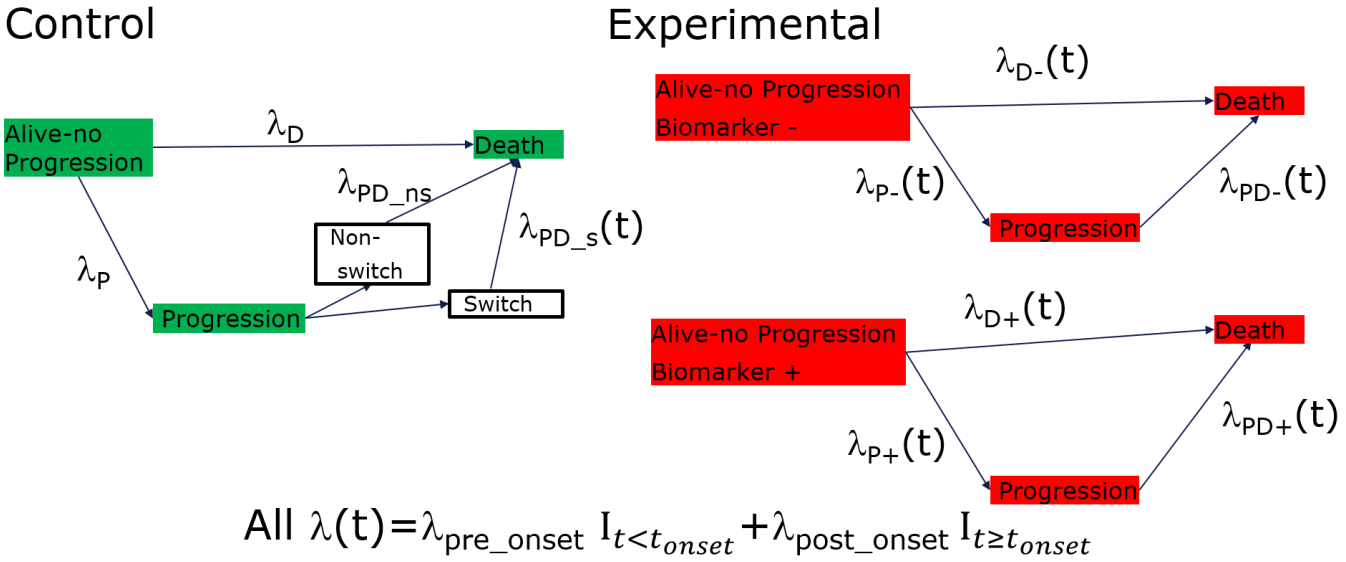
3-Arm RPSFT to adjust for treatment switching in superiority trials

Chen Y[1], Esmaeili H[1], Kupas K[2], Buchner H[1]
[1]*Staburo GmbH, Aschauer Str. 26b 81549 Munich, Germany*
[2]*Bristol-Myers Squibb, Arnulfstraße 29, 80636 Munich, Germany*

- We propose an enhanced RPSFT model for crossover correction of **3-arm trials**, with an adapted recensoring procedure for superiority trials and assess the performance on simulated data.
- The model estimates **2 acceleration factors**, one for the treatment effect and one for the alternative treatment effect.
- **eRPSFT improves the estimation** (especially precision) compared to a naïve ITT analysis and should be used to adjust for treatment switching in 3-arm superiority trials.

Delayed treatment effects, treatment switches and heterogeneous patient populations: how to design and analyse RCTs in oncology

Robin Ristl, Heiko Götte, Franz König, Martin Posch, Armin Schüler, Gernot Wassmer



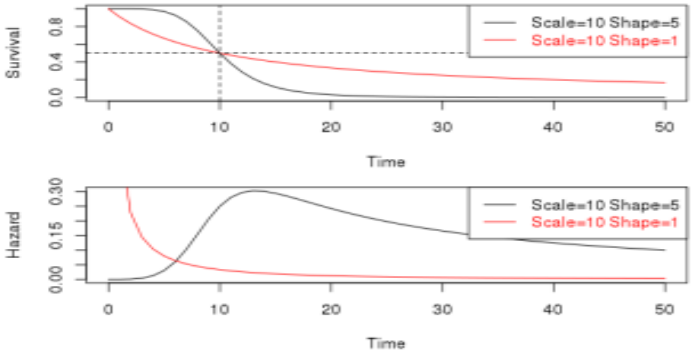
All $\lambda(t)=\lambda_{pre\_onset}\, I_{t<t_{onset}}+\lambda_{post\_onset}\, I_{t\geq t_{onset}}$

- Study survival and hazard functions in immune-oncology setting (different sources for non-proportional hazards)
- Study power of (weighted) log-rank tests
- Simulation results suggest a robust performance of maximum tests

Alternatives to comparing survival curves at the median

Dr. Jules Hernández-Sánchez
Roche Products Limited, Hexagon Place, Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK

- Two survival curves are commonly compared at the median survival time.
- However, they could be similar at the median but different everywhere else.
- A more comprehensive analysis should quantify differences better than just a comparison of medians.



Method	Estimate	Significance
δ	0.2	CI: -1.6 to 1.8
HL	0.14	CI: -0.44 to 0.43
LrT	NA	p=0
RMST	-3.2	p=0
GPC0	-0.007	p=0.85
GPC10	-0.2	p=0

δ: Difference of medians, HL: Hodges-Lehmann, LrT: Log-rank Test, RMST: Restricted Mean Survival Time, GPC0 (10): Generalised Pairwise Comparisons with 0 (10) Minimal Clincial Significant Difference

Doing now what patients need next

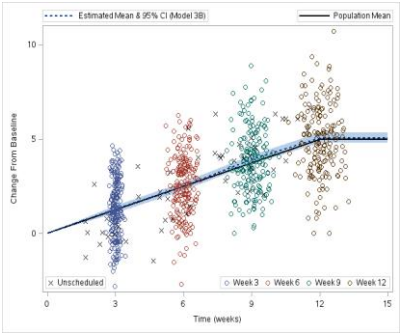
MODELLING LONGITUDINAL RESPONSES - DO WE NEED TO DEFINE VISIT WINDOWS?

Garcia-Hernandez A. Astellas Pharma Europe B.V. The Netherlands

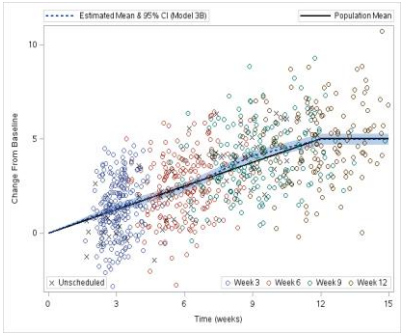
Poster
42

- This poster is a didactic-purposes exercise of interest for users of Mixed Models for Repeated Measurements (MMRM)
- I first illustrate how we can fit our usual MMRM (and get same fit & estimates!) using linear B-splines with knots at the planned visits to naturally provide predictions for the whole continuous time frame
- Later, I show how we alter slightly the above model to avoid that our estimates are influenced by lack of adherence of collection dates to the protocol schedule of visits
- I use simulations to assess the performance of standard MMRM versus marginal or conditional MMRM using linear B-splines

Good adherence



Poor adherence



astellas

Repeated measures using orthonormal polynomials in SAS

Patrick Lo, as part of research in statistics with Dr. William F. Scott at the University of Edinburgh

What
- Orthonormal polynomials can be applied to statistical analysis

Why
- Simplifying the computations of coefficients in an infinite series

How
- Transform original analysis algorithm with orthonormal polynomials then carried the same calculation steps required

Who
- All statisticians and researchers

When
- Can be applied on repeated measures analysis, using PROC GLM for example

Keywords for the poster:

Orthogonal polynomials, orthonormal polynomials, orthonormal transformation, repeated measures, within-subject univariate test, within-subject trend test, SAS, PROC GLM, pooled variance, sphericity assumption

For full SAS code and further details contact the author at patrick.lo@iqvia.com or +44 (0)118 450 6042.

What does SAS GLM output tell us?

	Timepoints		
Patient ID	Baseline	2h	4h
1	9	7	5
2	10	6	4
3	7	5	3
4	8	6	4
5	9	5	2
6	8	5	4
7	7	4	1
8	10	8	6
9	7	5	2
10	8	7	4

Pain scores of 10 patients assessed in 10-point visual analogue scale

- Results of univariate tests on within-subjects effects obtained from Z calculation agree with SAS PROC GLM results
- Results of polynomial trends in the within-subject factor considered a higher number of degrees of freedom in Z calculation, which therefore gives a higher F-statistic and a more precise estimate. SAS PROC GLM did not account for this

Multiple Imputation Strategies for Missing Continuous Outcomes in Non-Inferiority Randomized Trials

What is the poster about?

– NI trials with continuous outcomes where data are not collected following treatment discontinuation

– We explored operating characteristics of several multiple-imputation (MI) strategies to estimate both treatment policy and hypothetical strategies for handling treatment discontinuation

What did we do?

– Performed a simulation study comparing multiple imputation strategies:

(1) a standard treatment policy strategy (worsening drop-outs by the NI margin)

(2) a hypothetical strategy assuming MAR

(3) alternative treatment policy strategies (interior-family constraints)

What did we find?

– Worsening drop-outs by the NI margin was the most conservative in maintaining the type 1 error under the nominal threshold but suffered from large losses in power

– MI under MAR and one of the interior family constraints had good power and maintained the type 1 error well except in scenarios when the proportion of drop out on the experimental arm was large

Juan Abellan, Andre Acusta, Lin Taft & Douglas Thompson

Missing data strategy for the analysis of protocol-defined treatment failures in an asthma study

Judith Anzures-Cabrera, Roche, Welwyn Garden City, UK

- Asthma trial
- Treatment failures / rescue medication
- Missing data
- Strategies for dealing with missing data
- Interactions with Health Authorities

Assessment of tipping point analysis for handling various types of missing data (Poster 46)

Gareth James[1], Martin Clancy[2], Rosalind Hobson[2]
[1]Medical Statistics Consultancy, [2]PHASTAR

Tipping point analysis (TPA) is commonly used in trials to assess the sensitivity of results to deviations from the MAR assumption.

1. Traditional TPA is conservative as only penalises experimental arm. Should additional approaches also be considered?

2. Traditional TPA ignores any possible MNAR relationship in intermittent missing data.

3. Interesting patterns between p-value and increasing penalisation.

4. Delta (the measure of penalisation) is often difficult to interpret.
   - Can we identify a level that indicates the result is sensitive or not sensitive to missing data?
   - Can we make it more clinically interpretable?

Tips on Tipping Point

by Stephen Hope, Veramed Limited

"Missing data are a potential source of bias when analysing clinical trials. Interpretation of the results of a trial is always problematic when the proportion of missing values is substantial."

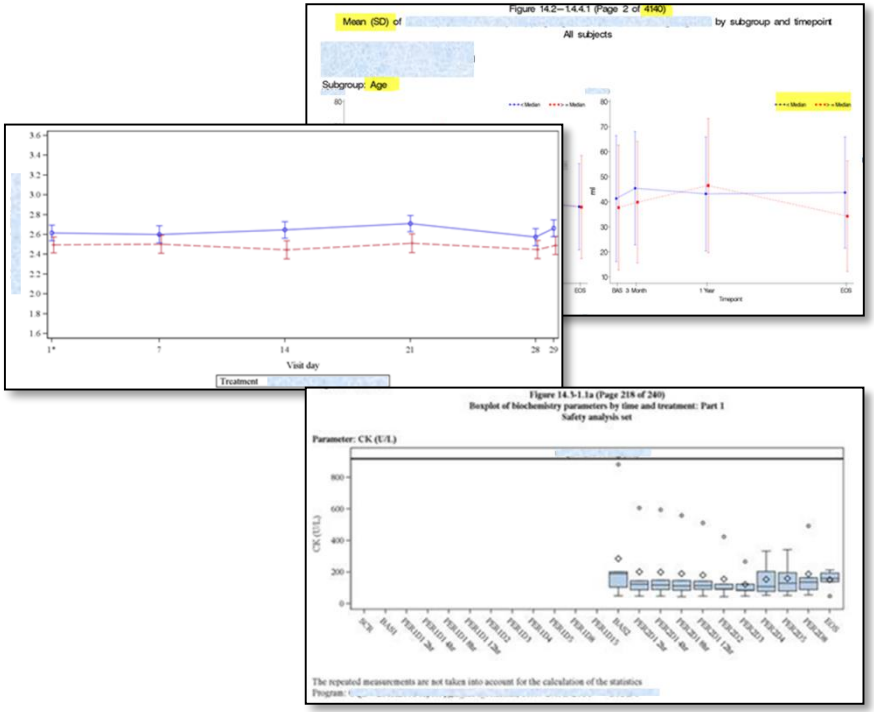
- EMA, Guideline on Missing Data in Confirmatory Clinical Trials; 2010

- Tipping point analyses can be used to investigate different assumptions about missing data using multiple imputation techniques
- The following practical aspects of tipping point analyses are discussed:
  - Model convergence
  - Run times
  - Quality control
  - Choosing appropriate increments for deltas
- Presentation of results and interpretation are considered

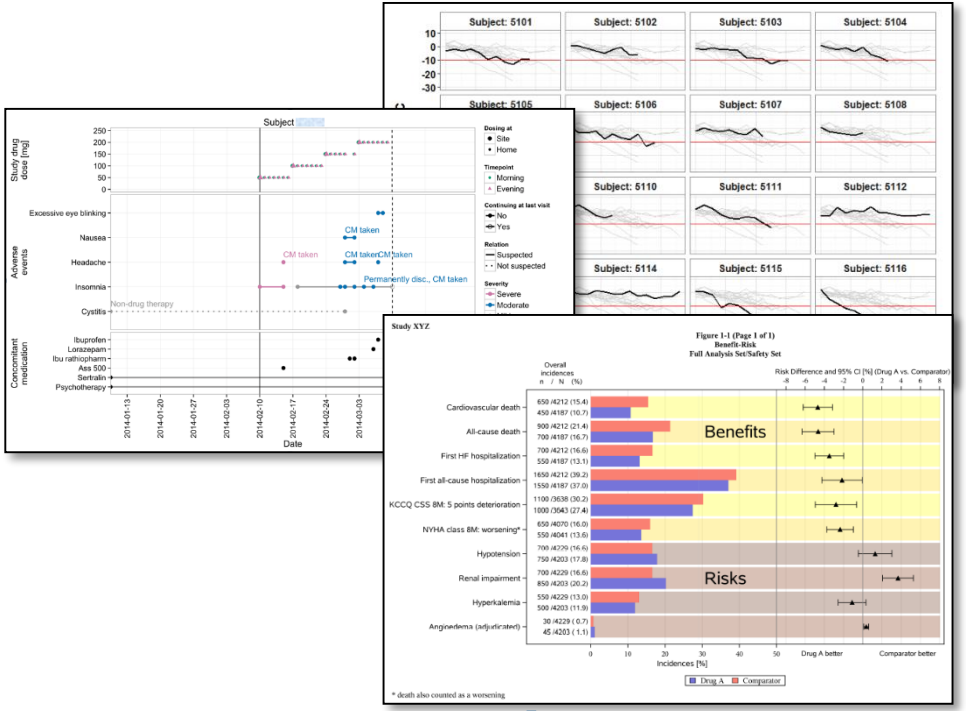
48. Graphical Principles Cheat Sheet

Authors: Mark Baillie, Alison Margolskee, Baldur Magnusson, Andrew Wright, Ruquan You, Ivan-Toma Vranesic, Julie Jones, Marc Vandemeulebroecke

Goal: see less of these...



...and more of these



NOVARTIS

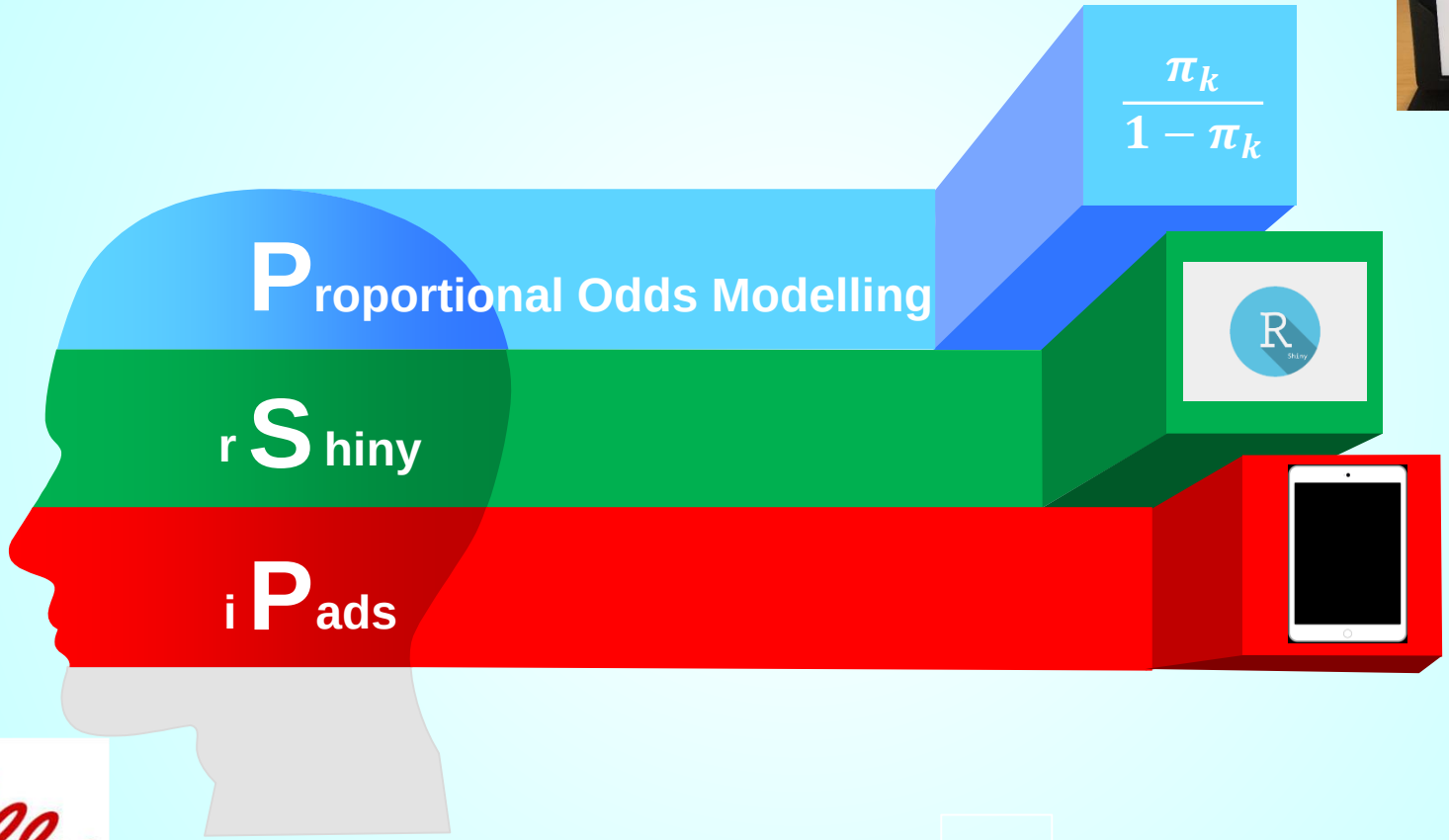
Shiny stats: Extending the reach of statistics through interactive applications

49

by Thomas Brown and Anastasiia Raievska, Veramed

- **R shiny**
- **2 Case Studies**
- **Recommendations on development and deployment of R Shiny apps**

A case study of interactive visualisations in a rare disease



Claire Brittain and Andrew McCarthy

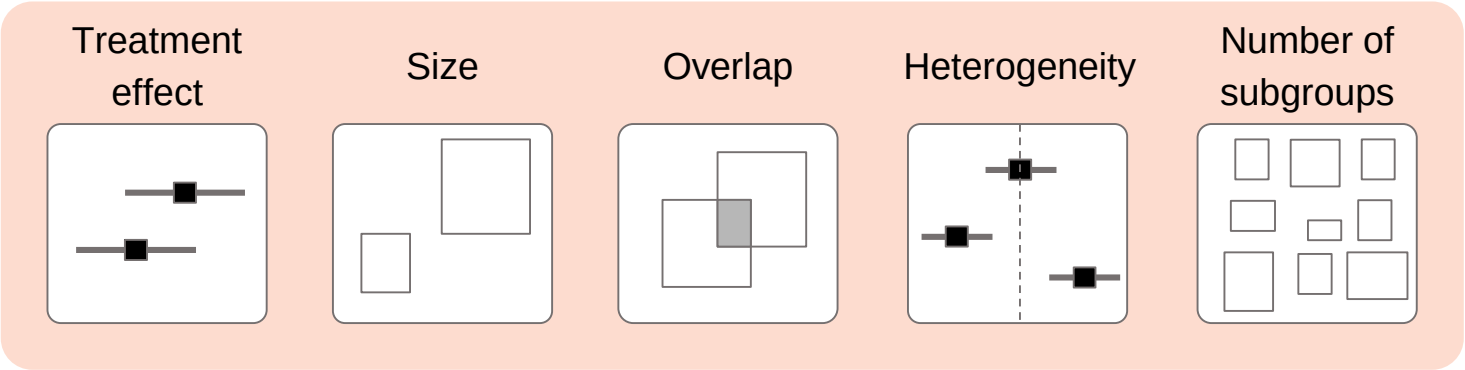
Graphical displays for subgroup analysis in clinical trials

51

Baseline characteristics may create a large number of subgroups.
Graphical approaches help to understand and communicate results from subgroup analyses to a wider audience.

Objective:

- Assess existing approaches based on a set of sensible criteria.
- Develop an effective visualization approach for subgroup analysis.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

MEDICAL UNIVERSITY OF VIENNA
Nicolas Ballarini, Yi-Da Chiu, Franz König, Martin Posch and Thomas Jaki
nicolas.ballarini@meduniwien.ac.at - www.ideas-itn.eu

The ROYAL MARSDEN
NHS Foundation Trust

By Mansour Sharabiani PhD

A Principled Approach to Single Predictor Cutpoint Selection to Identify Patients with a Defined Likelihood of Outcome in a Multi-Factorial Risk Prediction

APPLICATION OF JOINT DENSITY ESTIMATION AND MONTE CARLO SIMULATION

Expectation of Response Variable Condition of Feature Vector

$$f(c) \equiv Ep_c(x)[P(y = 1|x)] = \int P_c(x)P(y = 1|x)dx$$

$$c\,optimal = f^{-1}(p_0)$$

Monte Carlo Simulation

Bootstrapping

Joint Density Estimation

Cutpoint on one variable adjusted to multiple variables?

Life demands excellence

Poster #53

Population Enrichment – The Future of Drug Discovery

Author : Ankur Mukherjee

- Merck scored a point over Bristol Myers Squibb (BMS) in first line lung cancer immunotherapeutic trial.
- BMS studied the whole population instead of PDL1 positive patients only.
- I will explain why BMS failed and Merck succeeded by talking about adaptive enrichment design.

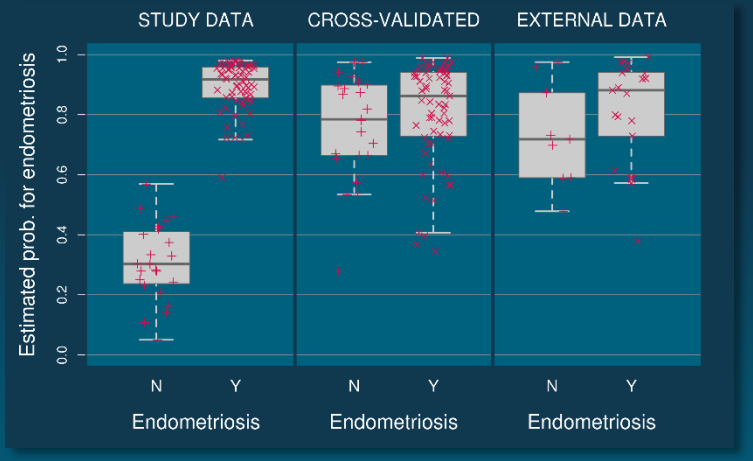
Cytel

Identification and external validation of gene expression signature as potential diagnostic biomarker for endometriosis

Poster #54

Anke Schulz[1], Sebastian Voss[2]

[1]Genomics & Biomarker Statistics, Bayer AG, Berlin, Germany
[2]Chrestos Concept GmbH & Co. KG, Essen, Germany



BACKGROUND

- 90 women, with 67 having confirmed endometriosis
- AIM: Identification of a potential diagnostic biomarker panel from genome-wide RNA expression

STATISTICAL METHODS

- Classifier construction with penalized logistic regression model (elastic net) on preselected variables (moderated t-tests)
- Performance estimation by 5-fold cross-validation (repeated 500 times)
- Classifier application to publicly available external data

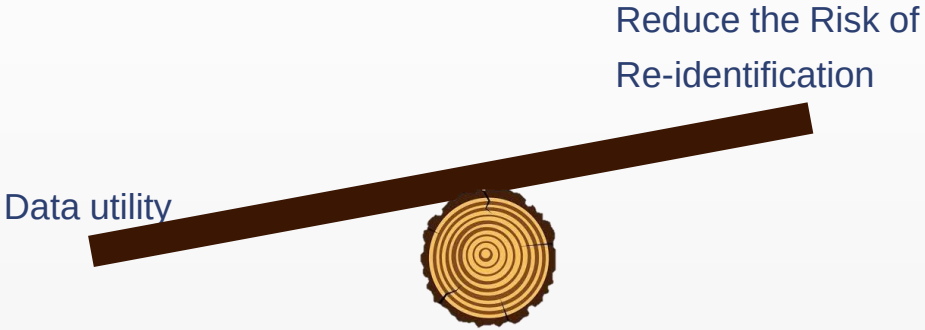
RESULTS:

- Differences in RNA expression in the eutopic endometrium not sufficient for a reliable classification
- Estimated classifier performance from the cross-validation confirmed by the external data, highlighting the value of cross-validation techniques

The Role of the Statistician in Data Anonymisation

Authors:
Parveen Kumar, Sr. Biostatistician
Kalpesh Prajapati, Sr. Biostatistician
Jeremy Wheeler, Director, Biostatistics

Poster Number:



About:

Introduction: Data Anonymisation
Need for Anonymisation
Identifiers in clinical trials data
Statistician's Role in Planning and Execution of Anonymisation
Statistician as a user of anonymized data

Event Forecasting – Poster 56

Abby Fuller[1] - Senior Biostatistician; Yann Poulouin[2] - Senior Biostatistician; Andrew Hartley[3] – Statistical Science Director

1. UK; 2. France; 3. United-States

- Simulate Event-Driven Trial Data
- Introduction to Forecasting Methods used at PPD
- Demonstration
- Presentation of Results and Overall Accuracy

KENYA - a new base for Pharmaceutical Statistics

Collins Mutua, Sally Hollis, Pamela Rennie, Nadeem Elahi

Poster Number 57

When asked about Kenya, you may think about:

- Wildlife safaris
- Tea
- Long-distance runners

Little is known about Kenya's talented pool of experienced and well-qualified statisticians and programmers

In 2016, using already established PHASTAR staff in Kenya, we set up an office in Nairobi to explore this potential

Now in our second year, the PHASTAR Kenya team are making valuable contributions to project teams

See our poster to find out more

A Guide to the Introduction to Industry Training (ITIT) Course

Promoting Statistical Insight

Sophie Dimonaco on behalf of the ITIT Committee:

Ruth Lowe, Alex Godwood, Gareth Thomas, Zelie Bailes, Anastasiia Raievska, Hoi-Shen Radcliffe & Sophie Hodge

- What is the ITIT course?
- Where and when is it happening?
- Who should go on it?
- What will I learn?
- How can I apply?

The Emergence of Statistical Leads #59

Sophie Hodge and Adam Webb, Manager Biostatistics, JENA Emerging Talent

IMS Health & Quintiles are now IQVIA™

Young (or new to the industry) statisticians. As you come to the end of your university career, do you have the complete skill set to become an effective statistician or programmer? Are our new graduate recruits getting the right exposure in their chosen courses? How do we address this - right opportunities at the right time, gradual exposure and shadowing of experienced staff? We've looked at the ways we have found to be most effective whilst trying to avoid 'too much too soon'.

The 'Emergence Matrix' – we've looked at skill sets and tasks that we might expect statisticians and programmers to be involved with and looked at how we can provide, measure and record these experiences.

Our feedback shows that there are still gaps in graduate skill sets:

- Many University courses focus on data analysis and reporting. Deriving new variables and formatting are rarely taught. How much SAS programming do statisticians really do and does this vary across the industry, or even within organisations. Do we treat graduate statisticians and programmers differently and should we?

- Have you ever felt a candidates knowledge and experience isn't reflective of their CV and length of service? Does this suggest lack of opportunity and training and mask the true potential the candidate has?

For further details please contact the author at adam.webb@iqvia.com or +44 (0)118 450 8641.