

Tuesday 20th November 2018 7:15 for 7:45

The Statistical Laboratory,
Centre for Mathematical Sciences,
Wilberforce Road, Cambridge, CB3 0WB

Bayesian and structural integration of background evidence in the design, analysis and interpretation of clinical trial data

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Abstract: Although background evidence always informs clinical study design, individual trial data are often first analysed in isolation and then meta-analysis is used to synthesise evidence accrued across multiple studies. However, in “small population” settings such as rare diseases, paediatric populations, or personalised/stratified medicine, the feasible sample size that can be recruited in each individual study typically falls short of that needed for a conventionally-powered trial. To address these limitations, we assess two avenues for integrated analysis of clinical data. First, we discuss the use of Bayesian informative priors based on relevant external data to increase the power and precision of such trials and propose a range of operating characteristics that can be useful to evaluate and compare designs. Here we present various prior and posterior summaries of the available historical, current and total evidence which can be used to help sponsors and regulators assess the strength of the prior assumptions and the extent to which the current trial data can influence the final posterior inference. We illustrate these methods through some recent case studies covering both paediatric settings borrowing efficacy data from adults, and in confirmatory trials in adults borrowing historical controls. Second, we explore the use of genetic annotation for design and analysis of biomarker-rich “large p , small n ” early phase oncology clinical trials. While the primary goal of these trials is to assess safety and preliminary clinical efficacy in a possibly heterogeneous patient population, a key secondary objective is to identify prognostic and predictive markers for design adaptation and for developing companion diagnostics. Here we focus on the analysis of associations between baseline gene expression and response to therapy, comparing the operational characteristics of bottom-up and top-down methods. While bottom-up methods use gene annotations for interpretation of the analysis results, top-down methods incorporate these background data within the structure of a hierarchical model likelihood for estimating pathway-level associations to clinical response. We show that, while top-down methods benefit from the advantages of parsimonious parametric modelling, they are not less exposed than bottom-up methods to a reliance on a knowledge basis that is both incomplete and in constant evolution.

Speakers: Nicky Best was an academic statistician for 20 years, starting out at the MRC Biostatistics Unit in Cambridge UK, before moving to Imperial College London, where she was Professor of Statistics and Epidemiology. She was Director of one of the research nodes of the UK Economic and Social Research Council National Centre for Research Methods from 2005-2011, and Biostatistics Theme Lead for the UK Medical Research Council Centre for Environment and Health. Her research interests focused around the development and application of Bayesian methods in health and social science, and her work in this area was recognised by the award of the Royal Statistical Society (RSS) Guy Medal in Bronze in 2004. Nicky is also a co-developer of the WinBUGS Bayesian software package. In 2014 Nicky moved to GlaxoSmithKline (GSK), where she is now Head of the Advanced Biostatistics and Data Analytics Centre of Excellence. In 2015, she co-lead a team of clinical statisticians at GSK that were awarded the RSS/PSI Award for Statistical Excellence in the Pharmaceutical Industry, for the implementation of formal Bayesian prior elicitation methods throughout all stages of drug development at GSK and use of these priors in making Go/No-Go design decisions. Nicky was also awarded the RSS Bradford Hill Medal in 2018 for her contributions to the exposition and application of Bayesian methods to clinical trials, cost-effectiveness, epidemiology and drug development programmes.

Fabio Rigat has been an academic statistician in the US (Duke), Netherlands (EURANDOM) and at the University of Warwick from 2000 to 2011. In 2011 he joined Novartis Vaccines and Diagnostics R & D as preclinical biostatistics group head, working on meningococcal (Bexsero®), maternal immunization (*group B Streptococcus*), influenza, *S.pneumoniae* and *S.aureus* investigational vaccine development programmes. In 2015 he joined GlaxoSmithKline Pharmaceuticals clinical development focusing in on immuno-inflammation within the Advanced Biostatistics and Data Analytics Centre of Excellence. From 2017 he works on design and integrated analysis of biomarker and clinical endpoints in oncology clinical trials.

Directions: The main entrance is reached from Clarkson Road by going along the footpath to the right of the Newton Institute, and turning left through the gatehouse towards the main building (Pavilion A), which has a glass front and a curved grassed roof. The main entrance is in the middle of the glass front. Coffee before the talk will be in the common room in Pavilion D, and the talk will be in Meeting Room 4 in Pavilion A. Free parking is available after 5pm on Clarkson and Wilberforce Roads.

Provisional Next Meetings (2019):

21st January – Sylvia Richardson (MRC Biostatistics).

4th February – Sian Evans (Public Health England).

25th February – Nicole Janz (University of Nottingham) on ‘Solving the Reproducibility Crisis’.

19th March – Graham Wheeler (UCL Cancer Trials Centre).

30th April – Matthew Bland (Institute of Criminology).

9th October – Imre Leader (Department of Pure Mathematics) on ‘Clueless Voting’.

Supper: Some members eat regularly in the University Centre before each meeting at **5-45pm**. Feel free to join them.

Subscriptions: of 1 pound are now due for attending the 2018-2019 session.

Secretary: Peter Watson, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 7EF; telephone 01223 273712; E-mail peter.watson@mrc-cbu.cam.ac.uk.

Slides and .mp3 files of old talks: <http://www.mrc-cbu.cam.ac.uk/people/peter.watson/csdg.html>

Approved Minutes of Annual General Meeting 2016-2017

The Annual General Meeting for the year 2016-2017 was held at the Cognition and Brain Sciences Unit on 10th October 2017. Present included: Ted Harding (in chair), Angelos Alexopoulos, Marion Chatfield, Jonathan Chuang, Tim Cole, Celine Cunen, Vuckovic Dragana, Gareth Funk, Zoubin Ghahramani, Shenghan Gao, Alex Hawkins-Hooker, Jules Hernandez-Sanchez, Peter Jacko, Edmund Jones, Stephen Kaptoge, Nelson Kinnersley, Jing Xuan Koh, Alexey Larionov, Kwut Sin Lee, Xin Lin, Kevin McConway, Bernard McKeown, Marieke Mur, Garabet Panikian, Jayantha Ratnayake, Joe Rennie, Emma Rocheter, Pantelis Samartsidis, Simon Schoenbuchner, Shaun Seaman, Maria Skoularidou, Colin Starr, Rosemary Tate, Jenny Thomas, Adam Wagner, Klaudia Walter, Peter Watson, Chris Wells, Lorenz Wermisch, Faye Williamson, Jing Xu, Yuejia Xu, Jie Yeo, Jing Hua Zhao. **Apologies:** Alun Bedding, Margaret Corbett, Mary Garratt, Martin Gibson, Clive Moncrieff, Pamela Morris, Haidee Philpott, Roger Sewell. The **minutes** of the previous A.G.M. were circulated and approved. The secretary reported a total attendance of 75 for the 2016-2017 session. Anyone with suggestions for speakers or venues or anyone interested in joining the committee please contact a committee member.

Treasurer's Accounts and Report 2016-2017:

The CSDG started the year in October 2016 with £43.73 cash in addition to £252.57 in the Cambridge Building Society. The table below shows the financial activity during the current year (Oct16 to Sept17).

Expenditure		Income	
Speakers' expenses	£44.85	Balance at Sep 2016	£43.73
Added to Bank a/c		Subscriptions	£46.00

Cash balance at 1st October 2016 £43.73, cash remaining 1st October 2017 £44.88. There is now £252.69 plus interest in a Community account at the Cambridge Building Society. The account holders are Ted Harding (current chairman), Peter Watson (current secretary) and Adam Wagner (current treasurer). These names can be changed on application. The principle holder is the treasurer. Any of the three account holders can deposit and withdraw money. It is suggested subscriptions remain at £1 for the 2017-2018 session.

Election of officers and committee: Committee for 2017-2018: *chair* Ted Harding; *secretary* Peter Watson; *treasurer* Adam Wagner; *officio* Dave Andrews; *ordinary* Martin Gibson, Haidee Philpott, Tony Sabin. **Any Other Business:** None.

Draft Minutes of Annual General Meeting 2017-2018

The Annual General Meeting for the year 2017-2018 was held at the Cognition and Brain Sciences Unit on 10th October 2018. Present: Ted Harding (in chair), Alex Baker, Matt Barclay, Sara Benitez Majano, Connie Chew, Nikos Demiris, Andrew Dillon, Ruben Drews, Josephine French, Mary Garratt, Martin Gibson, Mark Hill, Robert Kozarski, Trevor Lewis, Yoryos Lyratsopoulos, Holly Pavey, Adam Wagner, Sarah Walters, Peter Watson. **Apologies:** Margaret Corbett, David Culliford. The **minutes** of the previous A.G.M. were circulated and approved. The secretary reported a total attendance over 4 meetings of 83 for the 2017-2018 session. Anyone with suggestions for speakers or venues or anyone interested in joining the committee please contact a committee member.

Treasurer's Accounts and Report 2017-2018:

The CSDG started the year in October 2017 with £44.88 cash in addition to £252.69 in the Cambridge Building Society. The table below shows the financial activity during the current year (Oct17 to Sept18).

Expenditure		Income	
Speakers' expenses	£34.26	Balance at Sep 2017	£44.88
Added to Bank a/c		Subscriptions	£45.00

Cash balance at 1st October 2017 £44.88, cash remaining 1st October 2018 £55.62. There is now £252.69 (plus interest) in a Community account at the Cambridge Building Society. The account holders are Ted Harding (current chairman), Peter Watson (current secretary) and Adam Wagner (current treasurer). These names can be changed on application. The principle holder is the treasurer. Any of the three account holders can deposit and withdraw money. It is suggested subscriptions remain at £1 for the 2018-2019 session.

Election of officers and committee: Committee for 2018-2019: *chair* Ted Harding; *secretary* Peter Watson; *treasurer* Adam Wagner; *officio* Dave Andrews; *ordinary* Martin Gibson, Haidee Philpott, Tony Sabin. **Any Other Business:** None.