

Organised Session

Title: The use of multilevel modelling in economic evaluation alongside multinational trials

Organiser

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Chair: Prof. Mark Sculpher, Centre for Health Economics, University of York, mjs23@york.ac.uk

Chair Bio: Mark Sculpher is Professor of Health Economics and leader of the Programme on Economic Evaluation and Health Technology Assessment at the Centre for Health Economics, University of York (UK). He has been based at York University since 1997. Between 1988 and 1997, he worked at the Health Economics Research Group at Brunel University (UK), and during 1998 was a visitor in the Department of Clinical Epidemiology and Biostatistics at McMaster University in Canada.

He currently holds a Career Scientist Award in Public Health awarded by the UK NHS Research and Development Programme.

Mark has worked in economic evaluations of range of technologies including surgery for menorrhagia, angina and inguinal hernia; lasers; screening programmes for diabetic retinopathy and antenatal HIV infection; drug treatment for dyspepsia, asthma, menorrhagia and colorectal cancer; and hip replacement.

He also leads the economic component of York's contribution to health technology assessment reviews for the UK National Institute for Clinical Excellence (NICE). His methodological interests include incorporating patient preferences into benefit measures in economic evaluation, handling uncertainty and decision analytical modelling.

Mark is a member of the NICE Technology Appraisal Committee, and he chaired NICE's Task Group on methods guidance for economic evaluation. He is also a member of the Commissioning Board for the NHS Health Technology Assessment programme.

Discussant: Prof. Keith R Abrams, Centre for Biostatistics & Genetic Epidemiology, Department of Health Sciences, University of Leicester. keith.abrams@leicester.ac.uk

Discussant Bio: Keith R Abrams is Professor of Medical Statistics in the Centre for Biostatistics & Genetic Epidemiology, Department of Health Sciences, University of Leicester, having previously held posts at the London School of Hygiene & Tropical Medicine and King's College School of Medicine and Dentistry, London. His research interests include the development and application of Bayesian methods in bio-medical research and health-care evaluation, particularly within clinical trials, evidence synthesis, decision modelling and economic evaluation. Prof Abrams has co-

authored two books on *Methods for Meta-Analysis in Medical Research*, and *Bayesian Approaches to Clinical Trials and Healthcare Evaluation*, and has also co-edited a book on *Methods in Evidence-based Healthcare* arising out of the UK NHS HTA Programme.

Session Overview: Multinational trial-based economic evaluations analyse patient-level resource use and health outcomes data collected in different geographical locations, with the objective to produce a cost-effectiveness estimate that is generalisable between countries. However, decisions regarding the cost-effectiveness of healthcare technologies are essentially jurisdiction-specific.

It is widely recognised that a comparison of health services in different jurisdictions will reveal important differences in a range of economically-relevant parameters. These include clinical factors such as patient case-mix and clinical practice, but also economic variables including resource use and factor prices, whether centres in a particular country are technically efficient and preferences about health states. If countries vary markedly in these factors, this is likely to influence the resource use, unit costs and outcome data observed in the trial, resulting in the dataset taking on hierarchical characteristics. That is, there may be a correlation in the observed costs and outcomes relating to patients treated in the same location. In multinational trials the hierarchical nature of the cost-effectiveness data is an inevitable implication of the study design. In these cases, one of the assumptions underpinning the use of standard OLS regression - that the random errors, are independently distributed - does not hold, as observations within clusters will be correlated.

Unfortunately, although the key implication of clustering in economic data is that the cost-effectiveness of the interventions of interest may vary between countries, most multinational trial-based cost-effectiveness analyses (CEA) simply ignore this potential source of variability and assume that costs and health outcomes in the study do not differ greatly (at least in relative terms) across countries. Failure to acknowledge the hierarchical structure of the data in the analysis will result in exaggerated precision in the estimated cost-effectiveness results in the trial.

One natural analytical approach to handle hierarchical data structures is to use multilevel modelling (MLM). MLM has been successfully used in many fields of research. MLM provides not only a means for estimating country-specific measures of resource use, costs and cost-effectiveness, but also facilitates the correct quantification of sampling uncertainty around their point estimates by accounting for the variability in the results both within and between countries.

Moreover, MLM assists in the assessment of the generalisability by location of the CEA results by means of the shrinkage estimation which generates country-specific estimates of cost-effectiveness which are a weighted average of country-specific and trial-wide (pooled) data. Patient- and country-specific covariates can easily be incorporated in the analysis to explain between-country differences in cost-effectiveness results.

This session includes three papers that have recently proposed the adoption of MLM in trial-based CEA. The presentations will address the following key issues concerning the use and application of MLM for CEA:

1. The role of multilevel modelling in CEA alongside multinational RCTs: challenges and opportunities;
 2. The use of shrinkage estimation in the CEA of multinational clinical trials, and
 3. Multilevel models assessing international variation in cost and cost-effectiveness: the use of covariates.
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Abstract 1

Title: The role of multilevel modelling in cost-effectiveness analysis alongside multinational RCTs: challenges and opportunities

Presenting Author: Andrea Manca, Centre for Health Economics, Alcuin A/116, University of York, Heslington, York. am126@york.ac.uk

Presenting Author Bio: Mr. Manca is Research Fellow at the Centre for Health Economics (CHE), University of York, UK. He graduated from the University of Rome, Tor Vergata (Italy) with a BSc in Economics and holds an MSc in Health Economics from the University of York. His research interests include methodological and theoretical issues in the conduct of patient-level cost-effectiveness analysis in healthcare, with an emphasis towards the application of statistical methods in cost-effectiveness analysis and health outcomes research. Mr. Manca main research activity over the past five years has focussed on investigating methodological issues in the conduct of trial-based economic evaluation of healthcare interventions, topic in which he is currently completing his PhD. In 2003 Andrea was awarded a three-year Wellcome Research Training Fellowship in Health Services Research, to investigate problems concerning the generalisability by location of the results of cost-effectiveness analyses conducted alongside multinational and multicentre randomised controlled clinical trials collecting patient-level data.

Co-authors: Mark Sculpher, Centre for Health Economics, University of York, mjs23@york.ac.uk; Paul Lambert, Department of Health Sciences, Division of Epidemiology and Public Health, University of Leicester, pl4@leicester.ac.uk;

Abstract: In multinational trials the value of accumulating more, and perhaps more clinically representative, patients needs to be balanced against the requirement to establish the cost-effectiveness of the interventions for a particular decision maker whose interest focuses on one country. We recently proposed the use of multilevel modelling (MLM) as a framework to analyse cost-effectiveness data collected alongside multinational RCTs, showing its advantages compared to standard CEA methods. This work raised additional research questions concerning the optimal way to analyse cost-effectiveness data in an international context, and the role of *patient-* and *country-*specific covariates, in particular when the interest of the researcher is to derive country-specific measures of cost-effectiveness.

There are several approaches to MLM in multinational trial-based CEA. This presentation discusses the alternative modelling strategies, with the objective to highlight (i) their pro and cons, (ii) their use for policy-making, (iii) their practical implementation and opportunities for research, and (iv) challenges for applied economic research.

A more general Bayesian bivariate hierarchical modelling for multinational trial-based CEA is proposed. This approach allows flexible modelling of costs and effects in a multivariate framework, while facilitating the inclusion of *subjects* and *country-*specific covariates, in the attempt to explain observed variability in the economic data both *between-countries* and *between-patients* within countries.

The various methods will be illustrated using data from a large multinational trial which enrolled 3164 patients in 19 countries evaluating the cost-effectiveness of low-doses (n=1596) and high-doses (n=1568) of the ACE inhibitor Lisinopril in patients with chronic heart failure.

Abstract 2

Title: Shrinkage Estimation in the Cost-Effectiveness Analysis of Multinational Clinical Trials

Presenting Author: Andrew R. Willan, Sick Kids Research Institute and University of Toronto, andy@andywillan.com

Presenting Author Bio: Dr Willan is a biostatistician and clinical trial methodologist, and currently hold the positions of Senior Scientist in the Programme for Population Health at the Sick Kids Research Institute, Professor in the department of Public Health Sciences at the University of Toronto and Professor Emeritus in the department of Clinical Epidemiology and Biostatistics at McMaster University. He holds a PhD in biostatistics from the University of Western Ontario and an MSc in statistics from Queen's University at Kingston. His contributions to statistical methodology include publications in the areas of health economics, management trials, crossover trials, non-nested regression analysis and bivariate response models. Previously, Dr Willan held the posts of Head of Biometry of the Clinical Trials Programme at the National Cancer Institute of Canada and Head of Clinical Trials and Epidemiology for the Cancer Programme at Sunnybrook Medical Centre.

Co-authors: Eleanor M. Pinto, Sick Kids Research Institute and University of Toronto, eleanor.pinto@utoronto.ca

Abstract: Clinical trials of cost-effectiveness are often conducted in more than one country. The two most common ways of dealing with the multinational nature of the data are either to calculate pooled estimates of the differences in effectiveness and cost or to stratify results by country. Since the between-country heterogeneity is potentially substantial, pooled estimates may be difficult to interpret for any particular country. Policy decisions are often made at a national level, and so country-specific results are important. However, stratified country-specific analyses will be based on fewer patients and will often fail to provide adequate precision.

Shrinkage estimation is a compromise between these two approaches and has been used successfully in other fields. Shrinkage estimates, which are linear combinations of the pooled and stratified estimates, are country-specific yet less variable than those derived through a stratified approach. Multivariate (*i.e.* cost and effectiveness) shrinkage estimators depend on the method used to estimate the between-country variance. The various methods will be illustrated and compared using data from a multinational trial evaluating the cost-effectiveness of three thrombolytic drug regimens in patients with acute myocardial infarction.

Abstract 3

Title: Multilevel models assessing international variation in cost and cost-effectiveness: the use of covariates

Presenting Author: Richard Grieve, London School of Hygiene and Tropical Medicine, richard.grieve@lshtm.ac.uk

Presenting Author Bio: Richard Grieve is a lecturer based in the Health Services Research Unit at the London School of Hygiene and Tropical Medicine (LSHTM). He graduated from the University of Liverpool with a BA (Hons) in Economics and has an MSc in Health Economics from York University. He worked for four years at the GKT School of Medicine, in London before joining LSHTM in 1999. His main research interests are in the methodological issues facing economic evaluations. His PhD thesis uses microeconomic and statistical theory to understand variations in cost and cost-effectiveness across international health care settings. In 2003 Richard was awarded a four-year MRC fellowship to study reasons for cost variation, and the implications for economic evaluation.

Co-authors: Richard Nixon, MRC Biostatistics Unit, richard.nixon@mrc-bsu.cam.ac.uk; Simon Thompson, MRC Biostatistics Unit, simon.thompson@mrc-bsu.cam.ac.uk; Charles Normand, Trinity College, normandc@tcd.ie

Abstract: Patient and national-level covariates such as case-mix or the level spending on health care can be used in the design, analysis or interpretation of international economic evaluations. These covariates may be used to estimate cost-effectiveness for specific countries or patient groups. To estimate accurately the effect of these covariates on the costs and cost-effectiveness of different technologies, analytical methods are required that make plausible assumptions. Previous studies using ordinary least squares (OLS) models to identify covariates associated with cost variation, have assumed that individual observations are independent. However, multilevel models (MLMs), which accommodate the hierarchical structure of multinational data, may be more appropriate for estimating the effects and standard errors of different covariates.

This paper compares these different techniques using a multinational stroke dataset comprising case-mix, resource use, and cost data on 1300 stroke admissions from 13 centres in 11 European countries. OLS and MLMs with both normal and gamma distributions, estimated the effect of patient and national-level covariates on the total cost per patient, and on the incremental net benefit (INB) of a new, hypothetical intervention. The results from the OLS cost model, suggested that both patient and national-level covariates were associated with total cost, whereas the estimates from the MLMs showed that the level of health care spending was the only country-level variable associated with total cost. A meta-regression analysis found that the level of health care spending in each country was associated with variation in the INB, and provided a clear basis for stratifying the results of the cost-effectiveness analysis.

We conclude that using OLS models for assessing which covariates are associated with variation in costs and cost-effectiveness, can lead to incorrect inferences. Using MLMs to identify the covariates associated with variations in cost and cost-effectiveness across countries is more appropriate, and can inform the design, analysis and interpretation of multinational cost-effectiveness studies.
