Economics, Simulation Modelling and Diabetes: 9th Mount Hood Challenge 2018

German Diabetes Center

Düsseldorf, Germany

5th – 7th October 2018

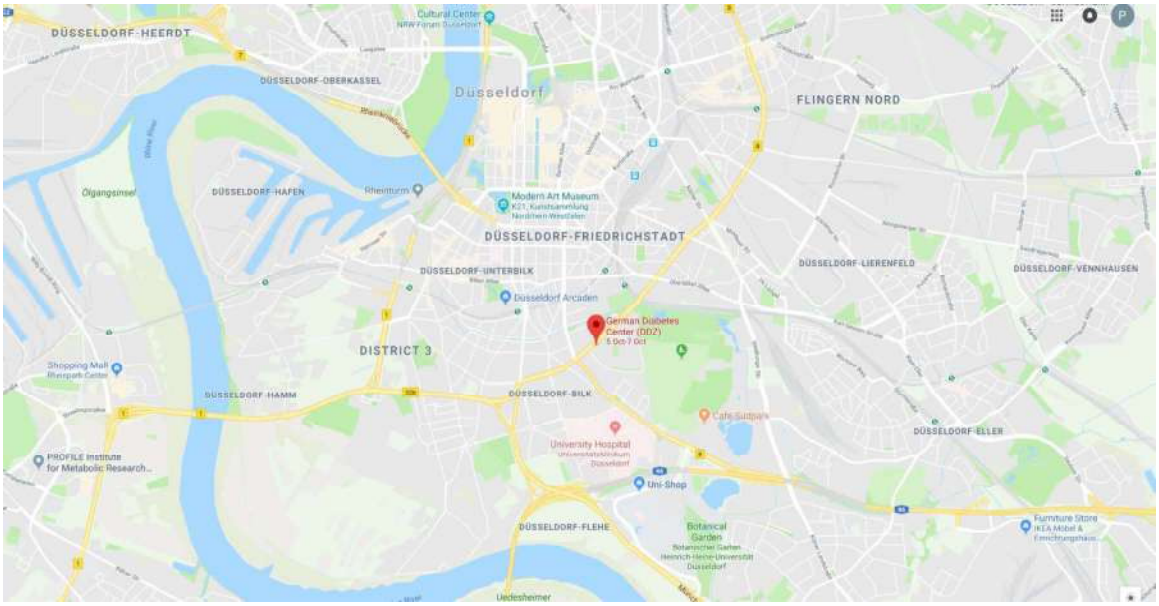
Contents

Economics, Simulation Modelling and Diabetes:

9th Mount Hood Challenge, Düsseldorf 2018

Conference Centre Map and General Information

Location: The conference will be held at the German Diabetes Center (Deutsches Diabetes-Zentrum, DDZ), Auf'm Hennekamp 65, 40225 Düsseldorf, Germany.



Registration for the optional pre-conference workshop will commence at 12.30pm on Friday, 5th October.

Registration for the conference will be from 8.15am onwards on Saturday, 6th October. The conference will conclude at 3.15pm Sunday, 7th October 2018.
There will be an optional session for representatives of modelling groups who are interested in contributing to the writing committee. This will take place immediately following the conclusion of the conference.

Conference registration includes lunches/refreshments and a conference dinner on the evening of 6th October.

Mount Hood Organising Committee 2018

Philip Clarke, The University of Oxford & The University of Melbourne

Jose Leal, The University of Oxford

Phil McEwan, Health Economics and Outcomes Research Ltd

Neda Laiteerapong, University of Chicago

Andrew Palmer, The University of Tasmania & The University of Melbourne

Michael Willis, The Swedish Institute for Health Economics

Michelle Tew, The University of Melbourne

The organising committee is chaired by Professor Philip Clarke, University of Oxford and this year's conference is being hosted by Dr Katherine Ogurtsova of the German Diabetes Center (DDZ).

Thanks are due to:

Katherine Ogurtsova, Karoline Mobers, Miriam Asche, Anja Viehmann, Ute Linnenkamp, Karoline Mobers and Andrea Icks for the local organisation; Mike Willis, Phil McEwan, Philip Clarke, Andrew Palmer and Mark Lamotte on developing the Challenges; Lei Si, Andreas Nilsson and Michelle Tew for compiling the challenges results and contributing to the program.

List of Participants

Elias	Altrabsheh	IQVIA
Christian	Asseburg	IHE The Swedish Institute for Health Economics
Jose	Bartelt-Hofer	Sanofi
Frauke	Becker	University of Oxford
Hayley	Bennett Wilton	Health Economics and Outcomes Research
Alexandra-Cristina	Bozocea	Hochschule Heilbronn
Michael	Brändle	Kantonsspital St. Gallen
Barnaby	Cheadle-Hunt	Ossian Health Economics and Communications
Gengshi	Chen	AstraZeneca
Philip	Clarke	University of Melbourne / University of Oxford
Ruth	Coleman	University of Oxford
Glenn	Davies	Merck & Co. Inc.
Charalabos-Markos	Dintsios	Heinrich-Heine-Universität Düsseldorf
Talitha	Feenstra	UMCG
Kurt	Fortwaengler	Roche Diabetes Care
Adam	Fridhammar	IHE The Swedish Institute for Health Economics
James	Gahn	Medical Decision Modeling Inc.
Alastair	Gray	University of Oxford
Jens	Gundgaard	Novo Nordisk A/S
Nino	Hallén	Novo Nordisk
Brian Bekker	Hansen	Novo Nordisk A/S
Bill	Herman	Univeristy of Michigan
Thomas	Hoerger	RTI International
Xinyang	Hua	University of Oxford
Elbert	Huang	University of Chicago
Andrea	Icks	Heinrich Heine University
Sachie	Inoue	CRECON Medical Assessment Inc.
Pierre	Johansen	Novo Nordisk A/S
Katharina	Kähm	Helmholtz Zentrum München GmbH - German Research Center for Environmental Health
MI Jun	Keng	University of Oxford
Seamus	Kent	University of Oxford
Josh	Knight	University of Melbourne

List of Participants (continued)

Shihchen	Kuo	University of Michigan
Neda	Laiteerapong	University of Chicago
Mark	Lamotte	IQVIA Consulting Solutions
Suzanne	Laplante	CADTH
Michael	Laxy	Helmholtz Zentrum München
Jose	Leal	University of Oxford
Karen	Lee	CADTH
James	Lewsey	University of Glasgow
Sandra	Lopes	Novo Nordisk A/S
Paula	Lorgelly	Office of Health Economics
Deanna	Marriott Isaman	University of Michigan
Julia	Meister	Hochschule Heilbronn
Liam	Mc Morrow	Health Economics Research Centre
Phil	McEwan	Health Economics and Outcomes Research
Robert	McQueen	University of Colorado
Andreas	Nilsson	IHE The Swedish Institute for Health Economics
Kirsi	Norrbacka	Eli lilly and Company
Solomon	Nuhoho	Johnson & Johnson Middle East
Anna	O'Donnell	University of Limerick
Katherine	Ogurtsova	German Diabetes Center (DDZ)
Beatrice	Osumili	Eli Lilly & Company
Huang-tz	Ou	National Cheng Kung University
Andrew	Palmer	University of Tasmania
Mafalda	Ramos	IQVIA
Stéphane	Roze	HEVA HEOR
Fabian	Sailer	HS Heilbronn
Iryna	Schlackow	University of Oxford
Wendelin	Schramm	Hochschule Heilbronn
Hui	Shao	Centers for Disease Control and Prevention
Lizheng	Shi	Tulane University SPHTM
Hidetoshi	Shibahara	CRECON Medical Assessment Inc.
Lei	Si	Macquarie University
Annabelle	Slingerland	Harvard/ MIT/ Joslin
Joel	Smith	University of Oxford

List of Participants (continued)

Harry	Smolen	Medical Decision Modeling Inc.
Centaine	Snoswell	The University of Queensland
Amarjeet	Tank	AstraZeneca
Michelle	Tew	University of Melbourne
An Duy	Tran	University of Melbourne
Christina	Tzogiou	Zurich University of Applied Sciences
Pieter	van Baal	Erasmus University Rotterdam
Michael	Willis	IHE The Swedish Institute for Health Economics
Chun-Ting	Yang	University of Michigan
Wen	Ye	University of Michigan
Ping	Zhang	Centers for Disease Control and Prevention

Pre-conference workshop

Diabetes simulation modelling through the looking glass

5 October 2018 from 1pm to 5pm

Oskar Minkowski-Saal, Ground floor, Old Building (Altbau, to the right from the entrance)

Outline

Introduction to diabetes modelling

- Brief History
- How simulation models work
- Constructing risk equations using individual data

Quality of life and complications

- Collection of Quality of life data: Case studies from UKPDS and ADVANCE studies
- How often and what do we need to collect?
- Heterogeneity in responses across regions
- Should be using levels or changes in Quality of life
- Relationship between utility and mortality
- Quality Adjusted Survival Models
- Role of meta-analysis
- What next?

Costs of treatments and complications

- Changes in the price and expenditure of diabetes therapies: recent evidence
- Options for collecting resource use information
- Analysis of costs in diabetes RCTS
- Costing equations – UKPDS Mk 1 & MK 2
- Sources of costing data in other countries – Sweden, Australia, ADVANCE.
- What next?

Future directions in modelling

- Adapting models across settings
- Calibration risk equations – Framingham indigenous example
- Developing new equations – mortality following events - WA UKPDS example
- LE calculators (Sweden & WA)

- What can we learn from meta-models?

New Developments in Type 1 diabetes

- Burden of the disease: Life expectancy gap in Sweden & Australia
- How a hypo can impact on your life expectancy
- Overview of a new Type 1 diabetes model
- What next?

Speakers

Professor Philip Clarke was instrumental in the development of both versions of the UKPDS Outcomes Model. More recently he has been involved in the development of a comparable Type 1 diabetes simulation model using data from a large diabetes registry in Sweden. He has also been involved with the economic analyses of the major diabetes clinical trials including the UKPDS, FIELD and ADVANCE studies.

P**rofessor Andrew Palmer** co-founded CORE, Centre for Outcomes Research, in July 2000 and was medical director and CEO until 2005. He developed the CORE diabetes model which has been widely used, particularly to evaluate pharmaceutical interventions for the treatment of Type 2 diabetes. He has since developed a diabetes prevention model and has collaborated with Prof Clarke on the development of the Type 1 diabetes model.

Economics, Simulation Modelling and Diabetes: 9th Mount Hood Challenge 2018

Conference overview

The Mount Hood Challenge conference focuses on economic aspects of diabetes and its complications. The challenges are developed collectively by an international group of researchers engaged in development of diabetes simulation models for health economic evaluation.

A major focal point of the conference will be a comparison of health economic diabetes models both in terms of their structure and performance. This conference builds on eight previous diabetes simulation modelling conferences that have been held since 1999.

This year's conference will focus on the economic aspects of diabetes and its complications and there will be three challenges that involve structured comparisons of predefined simulations undertaken by groups that have developed health economic models involving diabetes.

Speakers will include:

- **Paula Lorgelly,** Office of Health Economics & King's College, London.
- **Pieter van Baal**, Erasmus School of Health Policy & Management, The Netherlands.
- **Philip Clarke,** University of Melbourne, Australia & University of Oxford, UK.
- **Neda Laiteerapong,** University of Chicago, USA.

The conference will also have open sessions on all aspects of the health economics of diabetes.

Economics, Simulation Modelling and Diabetes: 9th Mount Hood Challenge 2018

Guest Speakers

Professor Paula Lorgelly

Paula is the Deputy Director of the Office of Health Economics and is a Visiting Professor at King's College London in the Division of Cancer Studies.

Prior to joining OHE in 2015 Paula was an Associate Professor at the Centre for Health Economics at Monash University (where she retains a visiting position).

Paula has over 15 years' experience working in academia in Australia and the United Kingdom (and a visiting position in Germany). Whilst in Australia she was a member of the Economics Sub-Committee of the Pharmaceutical Benefits Advisory Committee (PBAC), and in this capacity provided advice on the effectiveness and cost-effectiveness of treatments seeking reimbursement on the Pharmaceutical Benefits Scheme.

Associate Professor Pieter van Baal

Pieter van Baal is an Associate Professor of Health Economics at the Erasmus School of Health Policy & Management (ESHPM). He is an economist doing research within the field of health.

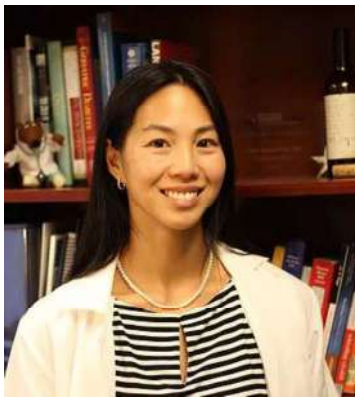
His research focuses on the methodology of cost effectiveness analysis, the relation between (non) medical consumption and population health and the modelling of chronic diseases in relation to risk factors. He has extensive experience in model based economic evaluations and statistical analyses. Before working at ESHPM he was employed by the National Institute for Public Health and the Environment (RIVM) where he was project leader of the RIVM Chronic Disease Model.

Professor Philip Clarke

Philip Clarke is Professor of Health Economics in Health Economics Research Centre, University of Oxford. He was formerly the Director of the Centre for Health Policy in the Melbourne School of Population and Global Health at University of Melbourne.

He has spent the best part of two decades working on the economics of diabetes, including the economic analysis of the United Kingdom Prospective Diabetes Study (UKPDS) and the development of simulation models for Type 1 and 2 diabetes. Since 2010 he has been Chair of the Mt Hood Diabetes Challenge Network.

He worked extensively on assessing the quality of life of people with diabetes and the implications for simulation models developing life-time outcomes such as Quality Adjusted Life Years.



Dr Neda Laiteerapong

Dr. Laiteerapong is a clinical investigator and internist at the University of Chicago who is committed to improving outcomes for patients with Type 2 diabetes by ensuring that they receive care that is personalized, timely, and addresses both physical and mental health.

She uses a wide range of health services research methods, including epidemiology, decision analysis, cost-effectiveness analysis, quality improvement initiatives, implementation science, surveys and qualitative analysis. Her work focuses on studying the implications of the timing of glycemic control over the life course on outcomes, prioritization of care for patients with type 2 diabetes, the intersection of health policy and the care of patients with chronic diseases, and the impact of chronic diseases on quality of life.

Conference Program

Day 1	Saturday 6th October 2018
Venue	*Oskar Minkowski-Saal and Paul Langerhans-Saal (adjoined), Ground Floor, Old building*
8:15-9:00am	**REGISTRATION**
9:00-9:10am	**Welcome –** Prof Andrew Palmer, University of Tasmania & University of Melbourne, Dr Katherine Ogurtsova and Prof Andrea Icks, German Diabetes Center (DDZ)
9:10-11:00am	**Challenge 1: Let's start thinking about tomorrow – How can diabetes models simulate the benefits of new therapies and technologies?** Chair: Mike Willis, IHE The Swedish Institute for Health Economics & Mark Lamotte, IQVIA Consulting Solutions & Lei Si, Macquarie University --- All modelling groups present a brief overview of their model --- BRAVO Model Cardiff Model CDC/RTI Model ECHO-T2DM (and ECHO-WM) IQVIA Core Diabetes Model MICADO Model MMD Model PROSIT Model SPHR CVD Prevention Model Treatment Transition Model UKPDS Outcomes Model
11:00-11:30am	**Tea and Coffee**
11:30am-12:30pm	**Plenary Session 1: Evaluation diabetes interventions within Europe: How much do national borders matter?** Speakers: Prof Paula Lorgelly, Office of Health Economics & A/Prof Pieter van Baal, Erasmus School of Health Policy and Management Chair: Prof Alastair Gray, University of Oxford
12:30-1:30 pm	**Lunch**

1:30-3:00pm	**Parallel session 1** Oskar Minkowski-Saal, Ground floor, Old building	**Parallel session 2** Paul Langerhans-Saal, Ground floor, Old building	**Parallel session 3** Josef-von-Mering-Raum, 2nd floor, New building
3:00-3:30pm	**Tea and Coffee**		
3:30-5:00pm	**Parallel session 4** Oskar Minkowski-Saal, Ground floor, Old building	**Parallel session 5** Paul Langerhans-Saal, Ground floor, Old building	**Parallel session 6** Josef-von-Mering-Raum, 2nd floor, New building
5:00- 6:00pm	**Business meeting: Where to next with Mt Hood?** Chair: Prof Philip Clarke, University of Oxford		
7:00pm onwards	**Conference Dinner at Hausmann's**		

Day 2	Sunday 7th October 2018
Venue	*Oskar Minkowski-Saal and Paul Langerhans-Saal (adjoined), Ground Floor, Old building*
9:10-10:30am	**Challenge 2: Quality of life and diabetes – How much does quality of life matter?** Chair: Prof Andrew Palmer, University of Tasmania & University of Melbourne --- Groups presenting challenge 2 results (Only new models to present) BRAVO Model Cardiff Model CDC/RTI Model ECHO-T2DM (and ECHO-WM) IQVIA Core Diabetes Model MICADO Model MMD Model PROSIT Model SPHR CVD Prevention Model Treatment Transition Model UKPDS Outcomes Model
10:30-11:00am	**Plenary Session 2: Growing old gracefully? The QALY at 50** Speaker: Prof Philip Clarke, University of Oxford Chair: Dr Annabelle Slingerland, Harvard/MIT/Joslin
11:00-11:30am	**Tea and Coffee**
11:30-12:30pm	**Challenge 3: Moving beyond diabetes – Comparing diabetes and non-diabetes simulation models** Chair: Prof. Philip Clarke, University of Oxford and A/Prof Neda Laiteerapong, University of Chicago --- Groups presenting challenge 3 results BRAVO Model ECHO-T2DM (and ECHO-WM) IQVIA Core Hypertension Model Scottish CVD Policy Model SHARP CKD-CVD Model SPHR CVD Prevention Model
12:30-1:30pm	**Lunch**
1:30-2:00pm	**Plenary Session 3: Using simulation models at bedside** Speaker: A/Prof Neda Laiteerapong, University of Chicago Chair: Michael Brändle, Kantonsspital St. Gallen
2:00-3:10pm	**Advances in diabetes simulation modelling – Focus on the development of pre-diabetes models** Chair: Dr Ping Zhang, Center for Disease Control and Prevention Speakers include: • Talitha Feenstra – Overview of pre-diabetes and diabetes prevention simulation models

	• Jose Leal – Pre-diabetes model using Chinese data • Chloe Thomas, Alan Brennan & Daniel Pollard – UK SPHR diabetes prevention model • Mark Lamotte – IQVIA Core Obesity model (with pre-diabetes and diabetes components) • Andrew Palmer – Australian pre-diabetes model • Josh Knight – Diabetes and pre-diabetes model using NZ PREDICT data • Xinyang Hua – Asian diabetes model using ADVANCE data • An Duy Tran – CVD/diabetes model for Australian Indigenous population
3:10-3:15pm	**Closing comments** Prof Philip Clarke
	Close (Afternoon coffee to finish)
3:15-4.00pm	Optional for representatives of modelling groups who are interested in contributing to the writing committee.

Instructions for presenters in conference sessions

- All presenters will have around 20 minutes each (including 5 minutes for questions).
- The time allocated for presentation will be 15 minutes. Allow a minimum of one minute per slide, preferably 2–3 minutes.
- A laptop computer and projector will be provided for your presentation, using Microsoft PowerPoint software. Both slides formats, 4:3 or 16:9, can be accommodated.
- Arrive at the meeting room before the session begins and contact the session convener for last-minute instructions or changes in the schedule.
- Please bring along your slides on a USB stick and load them onto the computer during the break before your session.
- During your presentation, state the purpose and objectives of the paper, the main concepts and results, and the conclusions. Avoid too much detail.
- Do not exceed the allocated time for your presentation.
- Presenters will be given an opportunity to make a pdf of a paper or slides available on the conference website.

Abstract sessions (room allocations)

Saturday 6th October 2018 (1:30 – 3:00pm)

Presenter	Authors	Title	Location (Chair)
Session 1 – Advances in simulation modelling			**Oskar Minkowski-Saal (Andrew Palmer)**
Deanna Isaman	Deanna JM Isaman, Wen Ye, William Herman	Modeling Incident Transient Ischemic Attack	
Christian Asseburg	Michael Willis, Andreas Nilsson, Christian Asseburg	Diabetic Kidney Disease (DKD) and Renoprotection in T2DM: An Underappreciated Driver of C-E in Economic Evaluation?	
Philip Clarke	Nina Wu, Bin Cui, Xinyang Hua, Andrew J. Palmer, Wang Lili, Philip Clarke	The Event Rate and Costs Associated with Major Complications of Diabetes in China: A Comparative Analysis	
Harry Smolen	Daniel R Murphy, Xueting Yu, Ian M Sturdy, Bradley H Curtis, Sinem Perk, Harry J Smolen	Validation of clinical outcomes from a type 2 diabetes pharmacoeconomic model using real world us electronic health record data: initial results and insights	
Session 2 – Type 1 diabetes mellitus			**Paul Langerhans-Saal (Talitha Feenstra)**
R. Brett McQueen	R. Brett McQueen, Cristy Geno, Marcelo Coca Perraillon, Kathleen Waugh, Jonathan D. Campbell, Marian Rewers	Projecting the Cost-Effectiveness of a Large Scale Diabetes Screening Program: Application to the Autoimmunity Screening for Kids (ASK) Program	
An Tran-Duy	An Tran-Duy, Josh Knight, Andrew J. Palmer, Ann-Marie Svensson, Bjorn Eliasson, Philip M. Clarke	Modelling progression of risk factors in patients with type 1 diabetes: towards the most appropriate functional forms for a simulation model of long-term health outcomes	
Josh Knight	An Tran-Duy, Josh Knight, Andrew J. Palmer, Ann-Marie Svensson, Bjorn Eliasson, Philip M. Clarke	A new type 1 diabetes model based on the Swedish Diabetes Registry	
Session 3 – Patient preferences/PROMS			**Josef-von-Mering-Raum (Alastair Gray)**
Charalabos-Markos Dintsios	Ch.-M. Dintsios, Markus Vomhof, D. Pesta, M. Apostolopoulou, J. Szendrödi, K. Müssig, M. Roden, A. Icks	Patients' preferences with regard to lifestyle interventions within HIT trial for diabetes mellitus	
Xinyang Hua	Xinyang Hua, Tom W.C Lung, Mark Woodward, Joshua A. Salomon, John Chalmers, Philip M. Clarke	Do self-rated health scores predict risk of all-cause mortality the same in patients with type 2 diabetes across different countries of the world?	
Michelle Tew	Michelle Tew, Michelle Dowsey, Peter Choong, Kim Dalziel, Philip Clarke	Health-reported quality of life following total knee replacement by diabetes status	
Lizheng Shi	Hui Shao, Shuang Yang, Vivian Fonseca, Charles Stoecker, Lizheng Shi	An Equation of Health Utility Decrements for Modelling of Diabetes Complications	

Abstract sessions (room allocations)

Saturday 6th October 2018 (3:30 – 5:00pm)

Presenter	Authors	Title	Location (Chair)
Session 4 – Advances in simulation modelling 2			
Thomas J. Hoerger	Thomas J. Hoerger	Development of U.S.-based Type 1 and Type 2 Diabetes Simulation Models	Oskar Minkowski-Saal (Jose Leal)
Jim Lewsey	Jim Lewsey, Claudia Geue, Robert Lindsay, David McAllister, Houra Haghpanahan, Sarah Wild	Developing a Scottish Type 2 Diabetes Policy Model and a web-based decision aid "dashboard"	
Michael Laxy	Verena M Schöning, Rolf Holle, Christoph Kurz, Annette Peters, Christa Meisinger, Wolfgang Rathmann, Michael Laxy	Performance of the UKPDS outcomes model V2.0 for prediction of death and cardiovascular events in patients with diabetes type 2 in Germany	
Talitha Feenstra	Talitha Feenstra, Eva Pagano, Liam McMorrow, Steef Konings, Daniela Di Cuonzo, Jose Leal	Validating the UKPDS Outcomes model in two independent datasets from Italy and the Netherlands	
Session 5 – Cost, outcomes and cost-effectiveness			
Mafalda Ramos	Ramos Mafalda, Volker Foos, Kristina Yu-Isenberg, Mark Lamotte	The relationship between poor adherence and HbA1c and weight changes in patients with type 2 Diabetes	Paul Langerhans-Saal (Neda Laiteerapong)
Mi Jun Keng	Mi Jun Keng, Apostolos Tsiachristas, Jose Leal, Alastair Gray, Borislava Mihaylova	Impact of variation in type 2 diabetes management on health outcomes and healthcare costs	
Mark Lamotte	Mark Lamotte, Volker Foos, Anastasia Ustyugova, Nikco Hau, Pranav Gandhi, Mafalda Ramos	Cost-effectiveness analysis of empagliflozin in comparison to sitagliptin and saxagliptin based on cardiovascular outcome trials	
Lei Si	Lei Si, You Wu, Xinyang Hua, Andrew J Palmer, Philip M Clarke	One-way sensitivity analysis in cost-effectiveness analyses in diabetes: which parameters are important?	
Session 6 – Challenges in simulation modelling			
Harry Smolen	Xueting Yu, Harry J Smolen	Using the treatment transition model to evaluate the effects of incorporating hba1c drift in oral anti-diabetic drugs for type 2 diabetes	Josef-von-Mering-Raum (Phil McEwan)
Joel Smith	Joel Smith, John Forbes, Anna O'Donnell	Identifying those who benefit from treatment: an open challenge for diabetes economic models	
Michael Willis	Michael Willis, Andreas Nilsson, Christian Asseburg	Challenges and Opportunities Associated with Modeling Cardioprotection in Economic Evaluation: Some Initial Reflections	
Wendelin Schramm	Wendelin Schramm, Fabian Sailer, Alexandra Bozocea, Julia Meister, Monika Pobiruchin	Costs and Consequences of Going Open Source with a Health-Economic Disease Model	

Mount Hood 2018 Challenges

Challenge #1: Cardiovascular Outcomes Challenge

I. Background and Objectives:

In recent years, a number of "so-called" cardiovascular outcomes trials (CVOT) have been published for a number of drug classes in type 2 diabetes. Evidence of benefit on hard outcomes for two classes, GLP1s and SGLT2s, is interesting because it cannot be explained entirely by effects on the traditional physiological parameters like HbA1c, SBP, and body weight that are the key determinants in widely used risk prediction equations such as the UKPDS Outcomes Model. As many diabetes models are based on these risk prediction equations, they are poorly fitted to predict the outcomes of these trials.

The purpose of this challenge is to examine the predictive accuracy of diabetes models on hard endpoints in two recent CVOTs and to examine whether recalibration can be used to better replicate CVOT results.

II. Simulation Overview:

You are asked to use your model to simulate the results of two recent CVOTs involving SGLT2s, EMPA-REG and the CANVAS Program (including 4 scenarios):

1. Replicate the EMPA-REG trial to the extent possible and simulate 3-year outcomes, separately by treatment arm (pooled 10mg and 25mg doses)
2. Calibrate, if your model allows, the model parameters to the outcomes in the placebo arm to the EMPA-REG trial and re-run for both study arms (document your methods)
3. Replicate the CANVAS Program to the extent possible and simulate 4-year outcomes, separately by treatment arm
4. Replicate the CANVAS Program to the extent possible and use the recalibrated model (constructed in Step 2) to simulate 4-year outcomes, separately by treatment arm

PDFs of key study publications are embedded at the end of this document. You may use any additional documents describing these studies that are in the public domain, but please do not use any non-public information. An Excel document, with 6 worksheets is provided to help you work through and document the parameterization of your model to match these simulations.

III. The Challenge Simulations:

1. **Replicate and simulate the empagliflozin and placebo arms of EMPA-REG**
   A. Read the EMPA-REG PDFs

B. Familiarize yourself with the accompanying Excel document (all worksheets) and:

   i. Describe the health states in your model on the worksheet "Health States" and the degree of match with EMPA-REG and CANVAS Program outcomes on the "Best Health State Match" worksheet

   ii. Describe the baseline patient characteristics required for your model on the worksheet "Baseline Patient Characteristics"

C. Load your model using the embedded EMPA-REG PDFs, other publicly available data, and assumptions and document it in the Excel worksheet ("Input Characteristics" and "Efficacy"). The empagliflozin and the placebo arms should be simulated separately.

   i. Baseline patient characteristics should reflect the EMPA-REG study population. Many of the baseline patient characteristics from EMPA-REG are reproduced in the Excel workbook on Worksheet "Input Characteristics" for the pooled trial population. Use values pooling the placebo and empagliflozin study arms, where possible if you source data elsewhere. If other parameters are required, use the best available data and document data sources and assumptions in the Excel workbook.

   ii. Initial biomarker changes and parameter drifts should be modelled so as to best match the EMPA-REG trial and the specifics of your model. If anti-hypertensive and anti-dyslipidemia agent treatment patterns are a key feature in your model, consider modelling the (relatively limited) data available on treatment evolution in EMPA-REG.

D. Run the simulations of the empagliflozin and the placebo arms for a period of 3 years (median in EMPA-REG was 3.1 years), if your model allows. Otherwise run the simulations for the closest period (and considering interpolating values to get figures relevant for 3-year study follow-up).

E. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD), major atherosclerotic cardiac events (MACE), coronary revascularization, transient ischemic attack (TIA) and enter in "EMPA-REG Outcomes" in the accompanying workbook.

F. If you have multiple sets of risk prediction equations (i.e., UKPDS 68 and UKPDS 82), please repeat the experiment and report the results using each of the different alternatives.

2. If your model permits risk adjustment for the key outcomes in EMPA-REG (whether via relative risk reductions, direct multipliers, direct manipulation of the risk equations, or other means), please recalibrate your model as follows:

A. Recalibrate model to predict the results for the placebo arm of EMPA-REG as closely as possible (do not adjust for empagliflozin arm) and re-run simulations

   i. Use the simulated results from the placebo arm in Step 1 to recalibrate the model to better fit the results of EMPA-REG using whatever options your model includes and appropriate techniques. Document the technique used to calibrate the model, as well as actual parameter values.

   ii. Use same settings as in Step 1, except please use recalibrated parameters (Note: in this simulation, the empagliflozin arm will be modelled using placebo-recalibrated risks)

   iii. Run the simulations for the same follow-up period as in Step 1, separately for each treatment arm

   iv. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, ESRD, MACE, coronary revascularization, TIA and enter in "EMPA-REG Outcomes" in the accompanying workbook. This gives a measure of how much of the observed empagliflozin treatment effects can be explained by changes in known risk factors and how much is unexplained (see embedded PDF "Kuo et al" for an illustration).

B. Recalibrate model to predict the results for just the empagliflozin arm of EMPA-REG as closely as possible and re-run simulations

   i. Use the simulated results from the empagliflozin arm in Step 1 to recalibrate the model to better fit the results of EMPA-REG using whatever options your model includes and appropriate techniques. Document the technique used to calibrate the model, as well as actual parameter values.

   ii. Use same settings as in Step 1, except the placebo arm will be modelled using the placebo-recalibrated risks and the empagliflozin arm will be modelled using the empagliflozin-recalibrated risks

   iii. Run the simulations for the same follow-up period as in Step 1, separately for each treatment arm

   iv. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, hospitalization for heart failure (HHF), hospitalization for angina, microalbuminuria, macroalbuminuria, ESRD, MACE, coronary revascularization, TIA and enter in "EMPA-REG Outcomes" in the accompanying workbook. This gives a measure of how well the results of

the trial (with many interdependent outcomes) can be replicated within the limitations of our models (with many moving parts). It also sets up the next challenge, where the recalibrations will be assessed in a different trial setting.

C. If you have multiple sets of risk prediction equations, calibrate and simulate only your "preferred" set. Indicate which set that was in the Excel workbook (Alternatively, please repeat the experiment and report the results using each of the different alternatives).

3. Replicate and simulate the canagliflozin and placebo arms of the CANVAS Program (using the uncalibrated model)

A. Read the CANVAS Program PDFs

B. Load your model using the embedded CANVAS Program PDFs, other publicly available data, and assumptions and document it in the Excel worksheet ("Input Characteristics" and "Efficacy")

i. Baseline patient characteristics should reflect the CANVAS Program study population. Many of the baseline patient characteristics from the CANVAS Program are reproduced in the Excel workbook on Worksheet "Inputs Characteristics". Use values pooling the placebo and canagliflozin study arms, where possible. If other parameters are required, use the best available data and document data sources and assumptions in the Excel workbook.

ii. Initial biomarker changes and parameter drifts should be modelled so as to best match the CANVAS Program and the specifics of your model. Consider modelling anti-hypertensive and anti-dyslipidemia agent treatment patterns in EMPA-REG if this is a key feature of your model.

C. Run the simulations for a period of 4 years (mean follow-up in CANVAS Program was 3.6 years), if your model allows. Otherwise run the simulations for the closest period (and considering interpolating values to get figures relevant for 3.6-years but indicate that you have done that).

D. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in "CANVAS Outcomes" in the accompanying workbook

E. If you have multiple risk prediction equations, please repeat the experiment and report the results using each of the different alternatives

4. Replicate and simulate the canagliflozin and placebo arms of the CANVAS Program using the model version that was recalibrated based on EMPA-REG results in Step 2 (<u>to the extent you are able</u>)

A. Estimate outcomes using just the placebo-recalibrated risks for both treatment arms (allows for estimation of how much of the observed empagliflozin treatment effects can be explained by changes in known risk factors and how much is unexplained (see embedded PDF "Kuo et al" for an illustration)

   i. Use same settings as in Step 3, except use the same recalibrated parameters from Step 2 for placebo arm

   ii. Run the simulations for the same follow-up period as in Step 3

   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in "Outcomes" in the accompanying workbook

B. Estimate outcomes using just the placebo-recalibrated risks for both treatment arms but applying direct HRs from CANVAS for the canagliflozin treatment arm ("CANVAS HRs" in the accompanying workbook). Because the hard outcomes are likely to be in part mediated by the corresponding changes in risk factors, this analysis provides an estimate of the magnitude of possible double-counting)

   i. Use same settings as in Step 3, except use the same recalibrated parameters from Step 2 for placebo arm

   ii. Run the simulations for the same follow-up period as in Step 3, applying HRs for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE for the canagliflozin arm (see ("CANVAS HRs" in the accompanying workbook)

   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF, amputations, and MACE and enter in "Outcomes" in the accompanying workbook

C. Using just the placebo-recalibrated risks for the placebo arm and the empagliflozin recalibrated risks for the canagliflozin arm (allows evaluation of how well recalibration translates across trials within a drug class, where patient recruitment differs)

   i. Use same settings as in Step 3, except use the recalibrated parameters from Step 2 for the placebo and empagliflozin arms separately for placebo and canagliflozin, respectively

   ii. Run the simulations for the same follow-up period as in Step 3

   iii. Extract the outcomes for any-cause death, CV death, nonfatal MI, nonfatal + fatal MI, nonfatal stroke, nonfatal + fatal stroke, HHF,

amputations, and MACE and enter in "CANVAS Outcomes" in the accompanying workbook

D. If you have multiple sets of risk prediction equations, calibrate and simulate only your "preferred" set. Indicate which set was used in the Excel workbook (Alternatively, please repeat the experiment and report the results using each of the different alternatives)

IV. Prepare an Overview/Discussion of your Key Findings

1. Prepare a brief document in Word (or some easily readable and widely accessible) format. Cover topics like:
   A. What was most difficult in parameterizing and running these scenarios?
   B. How did the unadjusted model perform? Absolute event risks? Relative treatment differences? LYs? QALYs?
   C. Was recalibration feasible? Useful? What was the impact on performance?
   D. If you have multiple sets of risk prediction equations:
      i. How did the results compare between risk equations? Did any capture the treatment effects without recalibration particularly well? Why?
      ii. Were any more/less amenable to recalibration?
      iii. Any general comments?
2. What did you learn from this challenge? Do you believe you can model these data credibly? Suggest possible ideas for improving model performance in predicting risks in T2DM with existing risk equations? Do you believe new risk prediction equations are warranted or can existing risk prediction equations be used (and possibly updated) into the future?
3. How to further model the cardiovascular risk
   A. How to predict after the study duration?
   B. How long to apply study effects?
   C. When to switch to next line of therapy?
   D. What will be the next line of therapy?

V. Prior to the meeting:

1. Submit the Excel results worksheet ("MH CHALLENGE 9 – Cardiovascular Outcomes Challenge_GROUP") to Philip Clarke at: philip.clarke@unimelb.edu.au by **September 21, 2018.**

Note: Please replace "GROUP" in file name to your group name before submitting.

2. Do not forget to submit the documentation (Section IV) including possible ideas for improving model performance in predicting risks in T2DM with existing risk equations and how to further model the cardiovascular risk

Appendix of relevant papers:

EMPA-REG

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa1504720
2. Supplementary Appendix This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa1504720
3. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34. DOI: 10.1056/NEJMoa1515920
4. Supplementary Appendix This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34. DOI: 10.1056/NEJMoa1515920
5. Fitchett D1, Butler J2, van de Borne P3, Zinman B4,5, Lachin JM6, Wanner C7, Woerle HJ8, Hantel S9, George JT8, Johansen OE10, Inzucchi SE11; EMPA-REG OUTCOME® trial investigators.Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J. 2018 Feb 1;39(5):363-370. doi: 10.1093/eurheartj/ehx511.
6. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™) https://cardiab.biomedcentral.com/articles/10.1186/1475-2840-13-102

CANVAS Program

7. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12.
8. Supplement to: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;376:644-57. DOI: 10.1056/NEJMoa1611925

Kuo et al (2018)

9. Kuo S1, Ye W2, Duong J3, Herman WH4.Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial. Diabetes Res Clin Pract. 2018 Jul;141:181- 189. doi: 10.1016/j.diabres.2018.04.040. Epub 2018 May 4.

Challenge #2: Quality of Life Challenge

Corrections and clarifications – 6 Sept 2018- in red

Motivation:

The purpose of this challenge is to examine the magnitude of impact of different aspects of quality of life on incremental health economics outcomes associated with common diabetes interventions. To ensure the simulations are relevant to common economic evaluations, the challenge will employ the average values for characteristics of patients enrolled in RCTs of common diabetes therapies. The average treatment effects will be modelled by permanent reductions in common risk factors including: (i) HbA1c; (i) systolic blood pressure; (iii) LDL cholesterol; and (iv) body mass index. Simulations will be undertaken for both men and women with the same characteristics.

This challenge is intended to form the basis of publication centred around understanding the elasticity of incremental estimated QALYs with respect to utility weights in diabetes models; i.e. the degree to which changes in utility weights affect QALYs.

The exercise will allow us to assess this by looking at what factors, and to what extent, have the greatest influence on incremental QALYs associated with common interventions used to treat people with diabetes.

An Excel spreadsheet accompanying these instructions (MH9 CHALLENGE – QOL.xlsm) is provided for the documentation of inputs and simulated outcomes.

Model Description:

We acknowledge that different models incorporate utilities in different ways (e.g. some assume additive effect, while others assume a multiplicative effect). However, for the purpose of this challenge, the **additive** quality-of-life (QoL) model is recommended when populating the health utility values into the simulation model. Suggestions on how utility values are applied are described in Appendix 1. If the additive QoL model is not feasible in your model, please document your assumptions how the health utility values are populated in your model.

For transparency it would be useful to describe how utilities are incorporated into different diabetes models. Please provide the following information in the accompanying Excel spreadsheet (in tab labelled "Model Description"). These will be used to form a table in the manuscript.

(i) What health states have a utility in your model;
(ii) What values are typically assumed for each health state (provide point estimates and/or ranges). If these have varied over time, what values were used in the most recent published economic evaluation that involved a QALY

simulation of the model. Please provide references of the source of the utilities where available.

(iii) In 150 words (or less) succinctly describe how quality of life is modelled (e.g. are changes in utilities assumed to have an additive or multiplicative effect on QALY outcomes).

Model Inputs:

Utility Values

To examine the effect of different assumptions regarding quality of life's impact on outcomes, we will run the same simulation with a variety of different assumptions regarding the utility associated with health states (such as diabetes-related complications). These values have been chosen to reflect high/low and average values from the literature. Utility values (Figure 1) from a recent systematic review (Beaudet et al., 2014) should be used for this challenge [Note suggestion for utility value for renal transplant in Appendix 1]. In this challenge, it would be adequate to use point estimates and not model 2nd order uncertainty.

If you require additional utility weights for health states not listed, please include these using values you currently use. Please document your sources and assumptions in the "Utility values" tab in the accompanying Excel spreadsheet.

Figure 1: Utility values used to populate model

Table 3 – Preferred utility values for modeling complications associated with T2DM.

Parameter	Proposed reference	Proposed utility value	95% CI	Range of candidate values
T2DM without complication	Clarke et al. [21]	0.785	0.681–0.889	0.690–0.940
Myocardial infarction	Clarke et al. [21]	−0.055	−0.067 to −0.042	−0.059 to −0.007
Ischemic heart disease	Clarke et al. [21]	−0.090	−0.126 to −0.054	−0.090 to −0.027
Heart failure	Clarke et al. [21]	−0.108	−0.169 to −0.048	−0.108 to −0.051
Stroke	Clarke et al. [21]	−0.164	−0.222 to −0.105	−0.164 to −0.070
Severe vision loss	Clarke et al. [21]	−0.074	0.124 to −0.025	−0.070 to −0.012
Amputation event	Clarke et al. [21]	−0.280	−0.389 to −0.170	−0.280 to −0.063
Peripheral vascular disease	Bagust and Beale [22]	−0.061	−0.090 to −0.032*	−0.186 to −0.061
Proteinuria	Bagust and Beale [22]	−0.048	−0.091 to −0.005*	One reference identified
Neuropathy	Bagust and Beale [22]	−0.084	−0.111 to −0.057*	−0.247 to −0.050
Active ulcer	Bagust and Beale [22]	−0.170	−0.207 to −0.133*	−0.206 to −0.016
Excess BMI (each unit above 25 kg/m²)	Bagust and Beale [22]	−0.006	−0.008 to −0.004*	−0.006 to −0.002
Hemodialysis	Wasserfallen et al. [23]	−0.164	−0.274 to −0.054*	One reference identified
Peritoneal dialysis	Wasserfallen et al. [23]	−0.204	−0.342 to −0.066*	One reference identified
Renal transplant	Kiberd and Jindal [26]	0.762	0.658–0.866	0.762–0.820
Cataract	Lee et al. [32]	−0.016	−0.031 to −0.001*	One reference identified
Moderate nonproliferative background diabetic retinopathy	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Moderate macular edema	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Vision-threatening diabetic retinopathy	Fenwick et al. [24]	−0.070	−0.099 to −0.041†	−0.070 to −0.012
Major hypoglycemia event	Currie et al. [18]	−0.047	−0.012‡	−0.020–0.005‡
Minor hypoglycemia event	Currie et al. [18]	−0.014	−0.004‡	−0.031 to −0.001†

CI, confidence interval; T2DM, type 2 diabetes mellitus.
* Estimated from the standard error values provided.
† Estimated from the interquartile range values provided.
‡ Disutilities converted into annual values.

Source: Table 3 from Beaudet et al. "Review of utility values for economic modeling in type 2 diabetes." Value in Health 17.4 (2014): 462-470 https://www.valueinhealthjournal.com/article/S1098-3015(14)00054-0/pdf

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 1. Any other baseline patient characteristics that your model may require can be sourced from publicly available literature (but please document this including sources in "Baseline Characteristics" tab in the accompanying Excel spreadsheet).

If possible, please email the covariate, covariate value, and suggested source in advance to Michelle Tew (michelle.tew@unimelb.edu.au), who can cumulate responses and redistribute to the groups to ensure greater standardization. This should be provided within 1 week of challenge instruction dissemination.

Table 1: Characteristics of a representative patient to be used in the simulations

Patient Characteristics	**Men**	**Women**
Current age	66	66
Duration of diabetes	8	8
Current/former smoker	N	N
HbA1c %	7.5	7.5
Systolic Blood Pressure mmHg	145	145
Diastolic Blood Pressure mmHg	80	80
Total Cholesterol mmol/l	5.2	5.2
HDL Cholesterol mmol/l	1.3	1.3
LDL Cholesterol mmol/l	3.0	3.0
BMI	28	28
Albumin: creatinine ratio	14.2	14.2
PVD	N	N
Micro or macro albuminuria (albuminuria ≥50)	N	N
Atrial fibrillation	N	N
eGFR (ml/min/1.73 m^2)	70	70
WBC (x10^9/l)	7	7
Heart rate (bpm)	79	79
Haemoglobin (g/dl)	14	14
Prior history of macrovascular disease	N	N
Prior history of microvascular disease	N	N

Source: ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline; see Appendix 2 for summary table

It is important in each simulation all other factors are kept constant between simulations and limit variation to the utility weights as per instructions in the steps below. This includes assumptions around biomarker evolution; i.e. HbA1c and systolic blood pressure to be kept constant over time and not allow for evolution.

The main outputs required will be incremental **undiscounted** QALYs. As such, please set the discount rate to 0% for QALYs prior to running the simulations.

Challenge Simulations:

Step 1: Run a simulation using the baseline characteristics in Table 1 held constant over a 40-year period, separately for males and for females

Extract the results and enter input values in a transparent manner in the accompanying Excel workbook in tab labelled "Time paths & Outcomes" (modify the workbook to fit your outcomes if necessary, but please try to preserve the basic structure). Do not forget to include traces (risk factor time paths) for input values of all the above risk factors; rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.), and life-expectancy.

For microsimulation models, please ensure that the number of replications is sufficient to generate stable results.

Step 2: Simulate four common interventions (plus all combined), separately for males and females

Re-run the simulation with four individual interventions (one-at-a-time and then all combined) that capture initial and permanent reductions in common risk factors from time paths modelled in Step 1. Reductions from these interventions should only be applied to post-baseline cycles and baseline values should remain unchanged.

(i) 0.5%-point reduction in HbA1c;
(ii) 10mm Hg reduction in Systolic Blood Pressure;
(iii) 0.5 mmol/l (19.33 mg/dl) reduction in LDL Cholesterol
(iv) 1-unit reduction in BMI (kg/m2)
(v) All interventions combined

Extract the results and add to the accompanying Excel workbook (in tab labelled "Time paths & Outcomes". Report outcomes and inputs in a transparent manner. Do not forget to include traces (numerical or curves) for input values of all the above risk factors; cumulative rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.) and life expectancy.

Step 3: Estimate incremental QALYs, separately for males and females

Using the "Proposed Utility Value" from Figure 1 run the baseline simulation and estimate expected QALY, assuming that decrements apply to the year of the event and

are similarly applied to each subsequent year. However, if temporary events/states such as hypoglycaemia are modelled, it is likely that these decrements only apply to the year of the event. If so, please document this.

Run each of the four interventions listed in Step 2 to estimate the expected QALYs and calculate the incremental QALYs compared to the baseline (control). Extract the results and add to the accompanying Excel workbook (in tab labelled "Time paths & Outcomes").

Step 4: Estimate incremental QALYs under different assumption regarding utility, separately for males and females

Repeat the simulation in Step 3 using different utility weights:

4.1 Low estimates of QALY: Use the lower limits of the 95% CIs for **All** utility values listed in Figure 1.

4.2 *High estimates of QALY*: Use the upper limits of the 95% CIs for **All** utility values listed in Figure 1

Step 5: Identify how much each utility value contributes to incremental QALYs

The final set of estimates will involve **only the first intervention (0.5%-point reduction in HbA1c).** It will involve varying each of the health state utility values in your model one at and time using the lower and upper limits of the 95% CIs to determine the sensitivity of incremental QALYs to changes in the utility value associated with each health state.

Step 6: (Optional)

Re-run Steps 1 and 2, but instead of using 0.785 for people without complications, use 0.681 (the lower limit of the 95% CI). Repeat this simulation for an intervention involving **0.5%-point reduction in HbA1c.** Record incremental QALYs for each change in utility compared to baseline (control).

Repeat the above in a second simulation using 0.889 (the upper limit of the 95% CI) and record incremental QALYs as per above.

Summary of findings:

Compile a summary of your findings in the accompanying Excel spreadsheet (in tab labelled "Summary"). Please complete the following.

A) Based on your results in Step 3, which intervention evoked the greatest change in incremental QALY?
B) Based on your results in Step 5, list three health states which evoked the greatest change in incremental QALY and the health state inducing the least change.
C) Provide an overview of what you learnt from this challenge.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MH CHALLENGE 9 – QOL Challenge_GROUP") to Mount Hood at: mthood2016@gmail.com by **September 21, 2018**. Please replace _GROUP with your modelling group name before submission.

APPENDIX 1

Incorporating health utility values for 2018 Mt. Hood Quality of Life challenge

Based on the 2018 Mt. Hood challenge conference call on September 5, 2018, two suggestions were made for the Quality of Life challenge, including:

1) The additive quality-of-life (QoL) model is recommended when populating the health utility values into the simulation model. As shown in Table 1 below, if a subject has experienced 2 different complications belonging to 2 different categories of disease (e.g., stroke [in the category of cerebrovascular disease] and myocardial infarction [in the category of coronary heart disease]), the health utility value will be reduced by 0.219 which is the sum of individual decrement for these 2 complications (i.e., 0.164+0.055). However, if a subject has experienced 2 complications within the same category of disease (e.g., myocardial infarction [in the category of coronary heart disease] and congestive heart failure [in the category of coronary heart disease]), the health utility value will be reduced by 0.108 (the decrement for heart failure) which is the largest decrement of these 2 complications. If the additive QoL model is not feasible in your model, please document your assumptions how the health utility values are populated in your model.

2) The utility decrement and its 95% confidence interval for renal transplant was assumed to be the half of those for hemodialysis.

Table 1. Categories of diseases/complications (summary from Figure 1 provided in the instructions for 2018 Mt. Hood Quality of Life challenge)

Disease category	Complication level provided in Mt. Hood QoL challenge	Utility value or decrement (95% CI) used for Mt. Hood QoL challenge
Baseline utility value	T2DM without complications	0.785 (0.681 to 0.889)
Acute metabolic disorder	Minor hypoglycemia event	-0.014 (-0.004)
	Major hypoglycemia event	-0.047 (-0.012)
Comorbidity	Excess BMI (each unit above 25 kg/m^2)	-0.006 (-0.008 to -0.004)
Retinopathy	Cataract	-0.016 (-0.031 to -0.001)
	Moderate non-proliferative background diabetic retinopathy	-0.040 (-0.066 to -0.014)
	Moderate macular edema	-0.040 (-0.066 to -0.014)
	Vision-threatening diabetic retinopathy	-0.070 (-0.099 to -0.041)
	Severe vision loss	-0.074 (-0.124 to -0.025)
Nephropathy	Proteinuria	-0.048 (-0.091 to -0.005)
	Renal transplant[1]	-0.082 (-0.137 to -0.027)
	Hemodialysis	-0.164 (-0.274 to -0.054)
	Peritoneal dialysis	-0.204 (-0.342 to -0.066)

Neuropathy	Peripheral vascular disease	-0.061 (-0.090 to -0.032)
	Neuropathy	-0.084 (-0.111 to -0.057)
	Active ulcer	-0.170 (-0.207 to -0.133)
	Amputation event	-0.280 (-0.389 to -0.170)
Cerebrovascular disease	Stroke	-0.164 (-0.222 to -0.105)
Coronary heart disease	Myocardial infarction	-0.055 (-0.067 to -0.042)
	Ischemic heart disease	-0.090 (-0.126 to -0.054)
	Heart failure	-0.108 (-0.169 to -0.048)

Abbreviations: QoL, quality of life; CI, confidence interval; T2DM, type 2 diabetes; BMI, body mass index.

[1]The utility decrement and its 95% confidence interval for renal transplant was assumed to be the half of those for hemodialysis.

Suggestions contributed by the Michigan Diabetes Modelling Group.

APPENDIX 2

ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline https://doi.org/10.1111/j.1464-5491.2005.01596.x

Table 1 Baseline characteristics of randomized patients (n = 11 140)

Characteristic	Mean (SD) or %
Mean age, years	66 (6)
Female, %	43
Mean duration of diabetes, years	8 (6)
Prior vascular disease	
History of major macrovascular disease, %	32
History of major microvascular disease, %	10
Other major risk factors	
Current smokers, %	14
Mean total cholesterol, mmol/l	5.2 (1.2)
Mean HDL cholesterol, mmol/l	1.3 (0.4)
Mean triglycerides, mmol/l	2.0 (1.5)
Mean albumin : creatinine ratio, μg/mg	14.2 [6.4–38.1]*
Mean body mass index, kg/m^2	28 (5)
Mean waist circumference, cm	99 (13)
Blood pressure control	
Mean systolic blood pressure, mmHg	145 (22)
Mean diastolic blood pressure, mmHg	81 (11)
History of hypertension, %	69
Current blood pressure lowering therapy, %	75
ACE inhibitors, %	43
Angiotensin-receptor blockers, %	5
Beta-blockers, %	24
Calcium antagonists, %	31
Thiazide/thiazide-like diuretics, %	14
Other diuretics, %	11
Other blood pressure lowering drugs, %	12
Glucose control	
Mean haemoglobin A_{1c} concentration, %	7.5 (1.5)
Diet-only treated diabetes, %	9
Current oral hypoglycaemic, %	91
Sulphonylurea, %	71
Metformin, %	61
Thiazolidinediones, %	4
Glinides, %	2
Acarbose, %	9
Current insulin†, %	1
Other major current treatments	
Aspirin or other anti-platelet, %	47
Lipid-lowering therapy, %	35

*Median and interquartile range presented as the distribution is highly skewed.
†Not prescribed as permanent or long-term therapy.

Challenge #3: Diabetes vs. Non-diabetes Simulation Models Challenge

Minor corrections and clarifications- 5 Sept 2018- in red.

The purpose of this challenge is to compare outcomes on four "representative" patient groups; with and without diabetes. To ensure the simulations are relevant to common economic evaluations, the challenge will employ the average values for characteristics of patients enrolled in RCTs of common diabetes therapies. Diabetes-specific models will run the same simulations in a separate challenge for people with diabetes only.

The average treatment effects will be modelled by permanent reductions in common risk factors including: (i) systolic blood pressure; (ii) LDL cholesterol; (iii) body mass index. Simulations will be undertaken for both men and women with the same characteristics.

An Excel spreadsheet accompanying these instructions (MH9 CHALLENGE – nondiabetes.xlsm) is provided for the documentation of inputs and simulated outcomes.

Model Description:

To allow comparisons across different models, it would be useful to describe your model. This includes type of model, health states, main disease modelled and how quality of life is incorporated. Please provide this information in the accompanying Excel spreadsheet (in tab labelled "Model Description").

Model Inputs:

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 1.

Table 1: Characteristics of a representative patient to be used in the simulations

Patient characteristic	Men	Women	Men	Women
	With diabetes		Without diabetes	
Age	66	66	66	66
Duration of diabetes	8	8	0	0
Current/former smoker	N	N	N	N
HbA1c %	7.5	7.5	5	5
Systolic Blood Pressure mmHg	145	145	145	145
Diastolic Blood Pressure mmHg	80	80	80	80
Total Cholesterol mmol/l	5.2	5.2	5.2	5.2

HDL Cholesterol mmol/l	1.3	1.3	1.3	1.3
LDL Cholesterol mmol/l	3.0	3.0	3.0	3.0
BMI	28	28	28	28
Albumin: creatinine ratio	14.2	14.2	14.2	14.2

Other relevant values can be assumed based on the literature (e.g. the above values are based on summary descriptive statistics from ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline https://doi.org/10.1111/j.1464-5491.2005.01596.x; see Appendix for summary table). Please document this including sources in "Baseline Characteristics" tab in the accompanying Excel spreadsheet.

It is important in each simulation all other factors are kept constant between simulations and limit variation as per instructions in the steps below.

Utility Values

Utility values (Figure 1) from a recent systematic review (Beaudet et al., 2014) should be used for this challenge. In this challenge, it would be adequate to use point estimates and not model 2nd order uncertainty.

If you require additional utility weights for health states not listed, please include these using values you currently use. Please document your sources and assumptions in the "Utility values" tab in the accompanying Excel spreadsheet.

Figure 1: Utility values used to populate model

Table 3 – Preferred utility values for modeling complications associated with T2DM.

Parameter	Proposed reference	Proposed utility value	95% CI	Range of candidate values
T2DM without complication	Clarke et al. [21]	0.785	0.681–0.889	0.690–0.940
Myocardial infarction	Clarke et al. [21]	−0.055	−0.067 to −0.042	−0.059 to −0.007
Ischemic heart disease	Clarke et al. [21]	−0.090	−0.126 to −0.054	−0.090 to −0.027
Heart failure	Clarke et al. [21]	−0.108	−0.169 to −0.048	−0.108 to −0.051
Stroke	Clarke et al. [21]	−0.164	−0.222 to −0.105	−0.164 to −0.070
Severe vision loss	Clarke et al. [21]	−0.074	0.124 to −0.025	−0.070 to −0.012
Amputation event	Clarke et al. [21]	−0.280	−0.389 to −0.170	−0.280 to −0.063
Peripheral vascular disease	Bagust and Beale [22]	−0.061	−0.090 to −0.032*	−0.186 to −0.061
Proteinuria	Bagust and Beale [22]	−0.048	−0.091 to −0.005*	One reference identified
Neuropathy	Bagust and Beale [22]	−0.084	−0.111 to −0.057*	−0.247 to −0.050
Active ulcer	Bagust and Beale [22]	−0.170	−0.207 to −0.133*	−0.206 to −0.016
Excess BMI (each unit above 25 kg/m²)	Bagust and Beale [22]	−0.006	−0.008 to −0.004*	−0.006 to −0.002
Hemodialysis	Wasserfallen et al. [23]	−0.164	−0.274 to −0.054*	One reference identified
Peritoneal dialysis	Wasserfallen et al. [23]	−0.204	−0.342 to −0.066*	One reference identified
Renal transplant	Kiberd and Jindal [26]	0.762	0.658–0.866	0.762–0.820
Cataract	Lee et al. [32]	−0.016	−0.031 to −0.001*	One reference identified
Moderate nonproliferative background diabetic retinopathy	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Moderate macular edema	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Vision-threatening diabetic retinopathy	Fenwick et al. [24]	−0.070	−0.099 to −0.041†	−0.070 to −0.012
Major hypoglycemia event	Currie et al. [18]	−0.047	−0.012‡	−0.020–0.005‡
Minor hypoglycemia event	Currie et al. [18]	−0.014	−0.004‡	−0.031 to −0.001‡

CI, confidence interval; T2DM, type 2 diabetes mellitus.
* Estimated from the standard error values provided.
† Estimated from the interquartile range values provided.
‡ Disutilities converted into annual values.

Source: Table 3 from Beaudet et al. "Review of utility values for economic modeling in type 2 diabetes." Value in Health 17.4 (2014): 462-470

Challenge Simulations:

The main outputs required will be expected and incremental **undiscounted** LE and QALYs. As such, please set the discount rate to 0% for LE and QALYs prior to running the simulations.

Step 1: Run a simulation for baseline characteristics of these patients over a 40-year period, separately for males and females

Extract the results and enter input values in a transparent manner in the accompanying Excel workbook in tab labelled “Time paths & Outcomes” (modify the workbook to fit your outcomes if necessary, but please try to preserve the basic structure). Do not forget to include traces (risk factor time paths) for input values of all the above risk factors; rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.), and life-expectancy and QALYs.

Step 2: Run a simulation of three common interventions

Re-run the simulation with three separate interventions that represented by a permanent decrement in common risk factors from time paths modelled in step 1:

(vi) 10mm Hg reduction in Systolic Blood Pressure;
(vii) 0.5 mmol/l reduction in LDL Cholesterol (for models with LDL parameter can assume a reduction in total of 0.5 mmol/l and no change in HDL).
(viii) 1-unit reduction in BMI

Reductions from these interventions should only be applied to post-baseline cycles and baseline values should remain unchanged.

As per Step 1, extract the results and add to the accompanying Excel workbook (in tab labelled "Time paths & Outcomes". Report outcomes and inputs in a transparent manner. Do not forget to include traces (numerical or curves) for input values of all the above risk factors; cumulative rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.) and life expectancy and QALYs.

Summary of findings:

Compile a summary of your findings in the accompanying Excel spreadsheet (in tab labelled "Summary"). Please complete the following.

D) Based on your results in Step 2, which intervention evoked the greatest change in incremental QALY?
E) Provide an overview of what you learnt from this challenge. Comment on the discrepancies in outcomes between patients with and without diabetes.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MH CHALLENGE 9 – NONDIABETES Challenge_GROUP") to Mount Hood at: mthood2016@gmail.com by **September 21, 2018**. Please replace _GROUP with your modelling group name before submission.

APPENDIX 1

ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline https://doi.org/10.1111/j.1464-5491.2005.01596.x

Table 1 Baseline characteristics of randomized patients (n = 11 140)

Characteristic	Mean (SD) or %
Mean age, years	66 (6)
Female, %	43
Mean duration of diabetes, years	8 (6)
Prior vascular disease	
History of major macrovascular disease, %	32
History of major microvascular disease, %	10
Other major risk factors	
Current smokers, %	14
Mean total cholesterol, mmol/l	5.2 (1.2)
Mean HDL cholesterol, mmol/l	1.3 (0.4)
Mean triglycerides, mmol/l	2.0 (1.5)
Mean albumin : creatinine ratio, μg/mg	14.2 [6.4–38.1]*
Mean body mass index, kg/m^2	28 (5)
Mean waist circumference, cm	99 (13)
Blood pressure control	
Mean systolic blood pressure, mmHg	145 (22)
Mean diastolic blood pressure, mmHg	81 (11)
History of hypertension, %	69
Current blood pressure lowering therapy, %	75
ACE inhibitors, %	43
Angiotensin-receptor blockers, %	5
Beta-blockers, %	24
Calcium antagonists, %	31
Thiazide/thiazide-like diuretics, %	14
Other diuretics, %	11
Other blood pressure lowering drugs, %	12
Glucose control	
Mean haemoglobin A_{1c} concentration, %	7.5 (1.5)
Diet-only treated diabetes, %	9
Current oral hypoglycaemic, %	91
Sulphonylurea, %	71
Metformin, %	61
Thiazolidinediones, %	4
Glinides, %	2
Acarbose, %	9
Current insulin†, %	1
Other major current treatments	
Aspirin or other anti-platelet, %	47
Lipid-lowering therapy, %	35

*Median and interquartile range presented as the distribution is highly skewed.
†Not prescribed as permanent or long-term therapy.

Models Participating in Challenges

- **Building, Relating, Assessing, and Validating Outcomes (BRAVO) of Diabetes Model**
- **Cardiff Model**
- **CDC/RTI Model**
- **ECHO-T2DM (and ECHO-WM)**
- **IQVIA Core Diabetes Model**
- **IQVIA Core Hypertension Model**
- **MICADO Model**
- **Michigan Model for Diabetes (MMD)**
- **PROSIT Disease Modelling Community (Framework)**
- **Scottish CVD Policy Model**
- **SHARP CKD-CVD Model**
- **SPHR CVD Prevention Model**
- **SPHR Type 2 Diabetes Treatment Model**
- **Treatment Transition Model (TTM)**
- **UKPDS Outcomes Model**

Building, Relating, Assessing, and Validating Outcomes (BRAVO) of Diabetes Model

Contact details of main developer:

Lizheng Shi, Tulane University [lshi1@tulane.edu]
Hua Shao [raistlinshao@gmail.com]
Vivian Fonseca [vfonseca@tulane.edu]

Model website: www.BRAVO4Health.com

Type of diabetes: Type 2 Diabetes

Brief Description:

The BRAVO diabetes model is a patient-level discrete-event microsimulation model. The core risk engine contains 3 separate modules (events module, risk factors module, and mortality module), each of which contains a series of regression equations to predict the occurrence of events, progression in risk factors, and mortality. Specifically, a total of 17 risk equations for predicting diabetes-related microvascular and macrovascular events (8 equations), hypoglycemia (2 equations), mortality (2 equations), and progression of diabetes risk factors (5 equations) are estimated using the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in the United States (n=10,251 patients). A globalization module was developed to calibrate the BRAVO model to other regions outside the United States.

Funding source for development of model: None

Key Publications:

Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). Pharmacoeconomics. 2018 May 3. [Epub ahead of print] PubMed PMID: 29725871.

Shao H, Yang S, Fonseca F, Shi L. Globalization Module for A Diabetes Progression Prediction Model: The Building, Relating, Acting, and Validating Outcomes (BRAVO) Model. Value in Health, 21, S5.

Cardiff Model

Contact details of main developer:

Phil McEwan, Health Economics Outcomes Research [Phil.McEwan@heor.co.uk]

Type of diabetes: Type 1/2 Diabetes

Brief Description:

The Cardiff Model is a fixed-time increment stochastic simulation model programmed in C++ and Visual Basic for Applications. It is designed to evaluate the impact of therapeutic intervention in Type 1 and Type 2 diabetes.

The Type 1 Diabetes Model utilises data from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study (microvascular complications) and the Swedish National Diabetes Registry (cardiovascular complications). The Type 2 diabetes model fully implements UKPDS 68 and 82 risk equations.

The model requires specification of demographic and established diabetes specific modifiable risk factors. In both Type 1 and Type 2 models, simulated patients are initialised with baseline profiles and, following the application of a treatment effect, are modelled over a lifetime. Pre-specified HbA1c threshold values, or a specified duration of therapy, may be used to invoke escalation to subsequent therapy lines (up to three in total).

Event costs are applied in the year of occurrence and maintenance costs applied in all subsequent years. The costs of diabetes-related complications are drawn primarily from UKPDS 65 or 84 and utilities from UKPDS 62, and supplemented with Type 1-specific data where published. The relationship between both weight change and the frequency and severity of hypoglycaemia on costs and quality of life is also captured.

Model output includes the incidence of microvascular and macrovascular complications, hypoglycaemia, diabetes-specific mortality and all-cause mortality and point estimates of costs, life years and quality adjusted life years in addition to probabilistic cost-effectiveness output.

Funding source for development of model: Funding for the development of the Cardiff Model was provided by AstraZeneca plc.

Key Publications:

McEwan P, Ward T, Bennett H, Bergenheim K. Validation of the UKPDS 82 risk equations within the Cardiff Diabetes Model. Cost Eff Resour Alloc. 2015.

McEwan P, Peters JR, Bergenheim K, Currie CJ. Evaluation of the costs and outcomes from changes in risk factors in type 2 diabetes using the Cardiff stochastic simulation cost-utility model. Current Medical Research and Opinion 2006.

McEwan P, Bennett H, Fellows J, Priaulx J and Bergenheim K. The Health Economic Value of Changes in Glycaemic Control, Weight and Rates of Hypoglycaemia in Type 1 Diabetes Mellitus. PlosOne 2016.

CDC/RTI Model

Contact details of main developer:

Centers for Disease Control and Prevention (CDC) and Research Trigeminal Institute (RTI), International.

Type of diabetes: Type 2 Diabetes

Brief Description:

The CDC-RTI Diabetes Cost-Effectiveness Model is a Markov simulation model of disease progression and cost-effectiveness for type 2 diabetes. The model has four modules: the main diabetes module, diabetes screening module, pre-diabetes module, and pre-diabetes screening module. The main diabetes module follows patients from diagnosis to either death or age 95 years and simulates development of diabetes related complications on three micro-vascular disease paths (nephropathy, neuropathy, and retinopathy) and two macro-vascular disease paths for diabetes screening and pre-diabetes. Model outcomes include disease complications, deaths, costs, and quality-adjusted life years (QALYs).

In the model, progression between disease states is governed by transition probabilities that depend on risk factors—including glycemic level (measured by HbA1c levels), blood pressure, cholesterol, and smoking status—and duration of diabetes. Interventions affect the transition probabilities and resulting complications. For example, tight glycemic control lowers HbA1c, slowing progression on the micro-vascular complication paths. With slower progression, fewer micro-vascular complications occur, deaths are delayed, QALYs increase, and the costs of complications are reduced. The model has been used to estimate the cost-effectiveness of many interventions/policy/guidelines related to diabetes prevention and cares, including treatment interventions for patients with diagnosed diabetes, screening for undiagnosed diabetes and pre-diabetes, and identifying high risk populations and utilizing lifestyle modification and drug therapies for type 2 diabetes prevention.

Funding source for development of model: Funding for the development of the model was provided by CDC.

Key Publications:

Hoerger, T.J., Segel, J.E., Zhang, P., and Sorensen, S.W. (2009). Validation of the CDC-RTI Diabetes Cost-Effectiveness Model. RTI Press publication No. MR-0013-0909. Research Triangle Park, NC: RTI International.

William H. Herman, MD, MPH; Thomas J. Hoerger, PhD; Michael Brändle, MD, MS; Katherine Hicks, MS; Stephen Sorensen, PhD; Ping Zhang, PhD; Richard F. Hamman, MD,

DrPH; Ronald T. Ackermann, MD, MPH; Michael M. Engelgau, MD, MS; and Robert E. Ratner, MD. The Lifetime Cost-Utility of Lifestyle Intervention or Metformin for the Prevention of Type 2 Diabetes Mellitus. Annals of Internal Medicine. 2005; 142:323-332.

Lin J, Zhuo X, Bardenheier B, Rolka DB, Gregg WE, Hong Y, Wang G, Albright A, Zhang P. Cost-effectiveness of the 2014 U.S. Preventive Services Task Force (USPSTF) Recommendations for Intensive Behavioural Counselling Interventions for Adults With Cardiovascular Risk Factors. Diabetes Care. 2017 May;40(5):640-646

ECHO-T2DM (and ECHO-WM)

Contact details of main developer:

Michael Willis, IHE The Swedish Institute for Health Economics [mw@ihe.se]

Model website: http://www.core-diabetes.com/

Type of diabetes: Type 2 Diabetes (and Chronic Weight Management)

Brief Description:

The Economic and Health Outcomes Model of T2DM (ECHO-T2DM) is a stochastic, micro-simulation (patient-level) model, suitable for estimating long-term cost-effectiveness of the treatment of T2DM. The physiology of T2DM is captured using Markov health states for micro- and macrovascular complications and death. ECHO-WM is a broader model of metabolic syndrome, of which ECHO-T2DM is an embedded sub-module. The model spans a broad set of obesity-related outcomes, including: pre-DM, T2DM, CVD, cancers shown to be linked to excess weight, and non-alcoholic steatohepatitis (NASH).

The cycle lengths of ECHO-T2DM and ECHO-WM are 1 year and the time horizons are user-definable. Both models account explicitly for both first-order and second-order uncertainty and are programmed in R with an Excel interface.

ECHO-T2DM/WM generates a user-defined number of hypothetical patients at simulation start based on user-defined probability distributions of glycemic status age, sex, ethnicity, disease duration, biomarker, smoking status, and health complications. Patient characteristics are updated each cycle.

Chronic kidney disease (CKD), neuropathy, and retinopathy are modeled in parallel. Progression rates, adjusted for HbA1c, T2DM duration and other biomarkers in line with current clinical understanding, steer transition between the different health states. Macrovascular complications consist of ischemic heart disease (IHD), myocardial infarction (MI), stroke, and heart failure (HF). Four sets of macrovascular risk equations are supported for ECHO-T2DM: UKPDS68, UKPDS82, ADVANCE, and the Swedish National Diabetes Registry. ECHO-T2DM supports UKPDS68 and UKPDS82 mortality risk equations, and mortality is a competing risk for all other events. Work is ongoing to estimate and include risk prediction equations using CANVAS Program data to improve the prediction of CV/Renal-protective agents in T2DM (e.g. SGLT-2s). Macrovascular and mortality risk for ECHO-WM are sourced from FHS, US life tables, and a study analyzing CHF discharge data.

Treatment comparisons consist of initial treatments (multiple comparisons are supported), treatment intensification sequences, HbA1c/BMI target values, and

treatment algorithms for hypertension, dyslipidemia, and excess weight. Anti-hyperglycemic drug profiles include initial biomarker changes (HbA1c, SBP, BMI, cholesterol, eGFR, and heart rate) and subsequent rate of biomarker evolution (i.e., "drift"), AE rates (e.g., hypoglycemia), relative risks for complications, treatment compliance, and discontinuation rules related to poor HbA1c control, AEs, contraindications, and/or reaching user-defined maximum treatment duration.

Unit costs for treatments, AEs, micro- and macrovascular complications (event costs and annual follow-up costs), revascularization procedures, and depression can be assigned. Indirect costs are supported. Baseline utility and disutility decrements for specific patient characteristics and health complications can be assigned.

ECHO-T2DM/WM reports outcomes including cumulative incidences and rates (RRRs) of each health outcome of health complications, AE rates (HRs), LYs and QALYs, inferred cause of death and sources of disutility, biomarker evolution curves, mean time to rescue treatment, and a host of cost and cost-effectiveness metrics.

Funding source for development of model: Janssen Global Services, LLC

Key Publications:

Neslusan C, Teschemaker A, Willis M, Johansen P, Vo L. Cost-Effectiveness Analysis of Canagliflozin 300 mg Versus Dapagliflozin 10 mg Added to Metformin in Patients with Type 2 Diabetes in the United States. Diabetes therapy. 2018 Apr;9(2):565-81.

Willis M, Johansen P, Nilsson A, Asseburg C. Validation of the Economic and Health Outcomes Model of T2DM (ECHO-T2DM). PharmacoEconomics 2017;35:375-396. DOI:

Sabapathy S, Neslusan C, Yoong K, Teschemaker A, Johansen P, Willis M. Cost-effectiveness of Canagliflozin versus Sitagliptin when Added to Metformin and Sulfonylurea in Type 2 Diabetes in Canada. J Popul Ther Clin Pharmacol. 2016;23(2):151-168.

Neslusan C, Teschemaker A, Johansen P, Willis M, Valencia-Mendoza A, Puig A. Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin Patients with Type 2 Diabetes Mellitus in Mexico. Value in Health Regional Issues 2015; 8C:8-19. DOI:

Willis M, Asseburg C, He J. Validation of Economic and Health Outcomes Simulation Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Journal of Medical Economics 2013; 16(8): 1007-1021.

IQVIA Core Diabetes Model

Contact details of main developer:

Mark Lamotte, IQVIA Consulting Solutions [Mark.lamotte@iqvia.com]

Model website: http://www.core-diabetes.com/

Type of diabetes: Type 1 & 2 Diabetes

Brief Description:

The IQVIA Core Diabetes Model CDM is a web-based diabetes policy analysis tool that performs real time simulations to predict clinical outcomes and costs for cohorts of patients with diabetes. Disease progression of patients is based on a series of inter-dependent Markov sub-models that simulate diabetes-related complications (angina, MI, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycaemia, ketoacidosis, nephropathy and end stage renal disease, neuropathy, foot ulcer and amputation).

Each sub-model uses time, state and diabetes type dependent probabilities derived from published sources, and utilizes tracker variables to overcome the memory-less properties of standard Markov models. The progression of relevant physiological parameters (e.g. HbA1c, SBP, lipids, BMI, etc.) is simulated based on long term epidemiological data and event risk is constantly updated based on the risk factors using risk equations.

The analysis modes in the model includes first and second order Monte Carlo simulations that can be performed on patient cohorts with either type 1 or type 2 diabetes, defined in terms of age, gender, baseline risk factors, pre-existing complications and comorbidities. The model is adaptable, allowing the inclusion of new clinical and economic data as they become available. The creation of country, health maintenance organization- or provider specific versions of the model is possible. Noteworthy, the model includes a detailed hypoglycaemia sub-module, alternative sets of contemporary risk equations including equations from the UKPDS82, the Swedish National Diabetes Register, Asian specific equations, the ADVANCE risk engine, PROCAM, the Fremantle-study and others. Moreover, the model can be easily calibrated to reflect the outcomes of cardiovascular outcomes trials. The type 1 section of the model incorporates the most recent epidemiological evidence. The reliability of simulated clinical outcomes has been tested with results validated against those reported from contemporary clinical trials and epidemiological studies.

The model is now available with a completely reworked web-based user interface that has been redesigned to be easy to use, facilitating the evaluation of the cost and clinical

impacts of diabetes treatments and strategies by users with varying levels of modelling expertise.

Funding source for development of model: IQVIA internal funding

Key Publications:

Foos V, Lamotte M, McEwan P. Contrasting predictions of cardiovascular incidence derived from alternative risk prediction models in type 1 diabetes. ISPOR 18th Annual European Congress held 7-11 November 2015 at the MiCo-Milano Congressi in Milan, Italy. PRM72.

Volker Foos, Mark Lamotte, Phil McEwan. Contrasting cost-effectiveness results derived from contemporary sets of alternative risk equations in type 2 diabetes. ISPOR 20th Annual International Meeting – Philadelphia 2015. presentation code: PRM23

McEwan, P., Foos, V., Palmer, J. L., Lamotte, M., Lloyd, A., & Grant, D. (2014). Validation of the IMS CORE diabetes model. Value in Health, 17(6), 714-724.

Palmer, A.J., Roze, S., Valentine, W.J., Minshall, M.E., Foos, V., Lurati, F.M., Lammert, M. and Spinas, G.A., 2004. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and costeffectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Current medical research and opinion, 20(sup1), pp.S5-S26.

Palmer, A.J., Roze, S., Valentine, W.J., Minshall, M.E., Foos, V., Lurati, F.M., Lammert, M. and Spinas, G.A., 2004. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Current Medical Research and Opinion, 20(sup1), pp.S27-S40.

IQVIA CORE Hypertension Model

Contact details of main developer:

Mark Lamotte, IQVIA Consulting Solutions [Mark.lamotte@iqvia.com]

Type of diabetes: Not applicable. However, presence of diabetes is an input in the model as well as complication.

Brief Description:

The IQVIA Core Hypertension Model (CHM) is a life-time Markov model developed in TreeAge with an Excel user interface. Yearly cycles are used. Events and health states considered are: type 2 diabetes, cardiovascular disease (acute coronary syndrome (ACS), stroke), heart failure and renal disease progressing to end stage renal disease.

Actual short-term effects of specific interventions on blood pressure, lipids, diabetes and smoking status are translated into long-term complications, using the published Framingham risk equation adapted to France for cardiovascular outcomes and other equations for development of diabetes, renal disease and heart failure.

The model is generic allowing the comparison of all types of therapies having an impact on blood pressure and cholesterol.

Funding source for development of model: Haute Authorité de Santé

Key Publications:

Gerlier L, Midy F, Lièvre M, Maurel F, Cohn E, Vellopoulou K, Lamotte M. Assessing the cost-effectiveness of the recommended antihypertensive drug classes in France using a lifetime Markov model. ISPOR US conference June 3-8 2012, Washington DC. CVD46.

Gerlier L, Midy F, Lièvre M, Maurel F, Cohn E, Vellopoulou K, Lamotte M. A lifetime cost-effectiveness analysis of the recommended antihypertensive drug classes in France. 9th HTAi Annual Meeting. HTA in Integrated Care for a Patient Centered System, Bilbao from 23 to 27 June 2012. Poster 363

MICADO Model

Contact details of main developer:

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Amber van der Heijden [A.vanderHeijden@vumc.nl]

Type of diabetes: Type 1 and 2 Diabetes

Brief Description:

MICADO (Modeling Integrated Care for Diabetes based on Observational data), is a simulation model for diabetes (type 2 and type 1), based in the RIVM Chronic Diseases Model (CDM). MICADO is a state transition model, accommodating dynamic populations as well as cohorts. Transitions are age, gender and risk factor level specific. The model was constructed using Mathematica software package version 6.1 (Wolfram Research) for Windows.

MICADO is a diabetes specific module of the CDM and as such a public health model, designed to evaluate the impact of interventions targeting risk factors for incidence and prognosis in diabetes mellitus. The incidence, prevalence and mortality of macrovascular diseases are extensively modelled based on data from large countrywide GP registries. Risk factors modelled are BMI, smoking, HbA1c, total cholesterol, and systolic blood pressure. Diabetes related microvascular comorbidities in lower extremities, eyes and kidneys are modelled to depend on HbA1c level.

MICADO's incidence and prevalence of complications as well as mortality were estimated from representative national registries, mainly GP registries. Risks were from systematic literature reviews. Most model parameters are age, and gender specific. This makes the model specifically fit for evaluating interventions at a population level, since the results will reflect a typical Dutch diabetes population. Users can define scenarios that specify levels of disease stages at baseline, risk factor levels or trajectories, and/or transition rates between disease stages.

Event costs are applied in the year of occurrence and maintenance costs applied in all subsequent years. The costs of diabetes-related complications are drawn primarily from Dutch sources, while utilities are based on either UKPDS 62 or the Dutch part of the CODE2 study.

Model output includes the incidence of microvascular and macrovascular complications, mortality from macro-vascular complications and all-cause mortality and costs, life years and quality adjusted life years. A deterministic and probabilistic version of the model can be run.

Funding source for development of model: Funding for the development of MICADO was provided by a grant from ZONMW (the Dutch National Science Foundation)

Key Publications:

van der Heijden AA, Feenstra TL, Hoogenveen RT, Niessen LW, de Bruijne MC, Dekker JM, Baan CA, Nijpels G. "Policy evaluation in diabetes prevention and treatment using a population-based macro simulation model: the MICADO model." Diabet Med. 2015;32(12):1580-7.

van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes Care. 2009 Nov;32(11):2094-8.

Feenstra TL, van Baal PM, Jacobs-van der Bruggen MO, Hoogenveen RT, Kommer GJ, Baan CA. Targeted versus universal prevention. a resource allocation model to prioritize cardiovascular prevention. Cost Eff Resour Alloc. 2011 Oct 6;9(1):14.

Jacobs-van der Bruggen MA, van Baal PH, Hoogenveen RT, Feenstra TL, Briggs AH, Lawson K, Feskens EJ, Baan CA. Cost-effectiveness of lifestyle modification in diabetic patients. Diabetes Care. 2009 Aug;32(8):1453-8.

Management and Modeling of Diabetes and its complications. Amsterdam, November 2013. PhD Thesis. Amber van der Heijden.

Michigan Model for Diabetes (MMD)

Contact details of main developer:

Wen Ye, Michigan Diabetes Modelling Group, University of Michigan [wye@umich.edu]

Model website:

http://diabetesresearch.med.umich.edu/Core_MCDTR_Methods_DiseaseModeling.php

Type of diabetes: Type 2 Diabetes

Brief Description:

The Michigan Model for Diabetes (MMD) is a computerized disease model that enables the users to simulate the progression of diabetes over time, its complications (retinopathy, neuropathy and nephropathy), and its major comorbidities (cardiovascular and cerebrovascular disease), and death. Transition probabilities can be a function of individual characteristics, current disease states or treatment states. The model also estimates the medical costs of diabetes and its comorbidities, as well as the quality of life related to the current health state of the simulated subjects. MMD is implemented in a disease modeling software, Indirect Estimation and Simulation Tool, programmed in python language.

In contrast to other models, the transition probabilities implemented in the MMD were obtained by synthesizing the published literature. Most of the risk equations adapted in the coronary heart disease sub-model and cerebrovascular disease sub-model are from the UKPDS Outcomes Model I. Transition probabilities were derived by calibrating these risk equations to contemporary population-based epidemiologic studies and randomized controlled clinical trials.

MMD explicitly models diabetes management strategies and allows users to modify them to match the specific scenarios that they are simulating. Changes in risk factors (HbA1c, BMI, lipid profiles and systolic and diastolic blood pressures) over time in simulated individual patients are determined by both treatment states and aging/disease progression. MMD allows users to control risk factor changes by defining the enhancement thresholds for and adherence rates to treatment for hyperglycemia, dyslipidemia, and hypertension, and the adherence rate to smoking cessation and taking aspirin.

Funding source for development of model: National Institute of Diabetes and Digestive and Kidney Diseases

Key Publications:

Kuo S, Ye W, Duong J, Herman W. Are the Favorable Cardiovascular Outcomes of Empagliflozin Treatment Explained by Its Effects on Multiple Cardiometabolic Risk Factors? A Simulation of the Results of the EMPA-REG OUTCOME Trial. Diabetes Research and Clinical Practice. 2018;141:181-189.

Ye W, Brandle M, Brown MB, Herman W. The Michigan Model for Coronary Heart Disease in Type 2 Diabetes: Development and Validation. Diabetes Technol Ther. 2015;17:701-711.

Herman W, Ye W, Brown MB, Simmons R, Davies M, Khunti K, Rutten G, Sandbaek A, Lauritzen T, Borch Johnsen K, Wareham N. Estimating the public health impact of early detection of type 2 diabetes: a modeling study based on the results of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe). Diabetes Care. 2015;38:1449-1455.

R Li, D Bilik, MB Brown, P Zhang, SL Ettner, RT Ackermann, JC Crosson, WH Herman. Medical Costs Associated with Type 2 Diabetes Complications and Comorbidities. American Journal of Managed Care. 2013;19:421-430.

P Zhang, MB Brown, D Bilik, RT Ackermann, R Li, WH Herman. Health Utility Scores for Persons with Type 2 Diabetes in U.S. Managed Care Health Plans: Results from Translating Research into Action for Diabetes (TRIAD). Diabetes Care. 2012;35:2250-2256.

Ye W, J. Barhak J, Isaman DJM. Use of Secondary Data to Estimate Instantaneous Model Parameters of Diabetic Heart Disease: Lemonade Method. Information Fusion. 2012;13:137-145.

Barhak J, Isaman DJM, Ye W, Lee D. Chronic disease modelling and simulation software. Journal of Biomedical Informatics. 2010;43:791-799.

Isaman DJM, BarhakJ , Ye W. Indirect Estimation of a Discrete-State Discrete-time model using Secondary Data Analysis of Regression Data. Statistics in Medicine. 2009;28:2095-2115.

Zhou H, Isaman DJM, Messinger S, Brown MB, Klein R, Brandle M, et al. A Computer Simulation Model of Diabetes Progression, Quality of Life, and Cost. Diabetes Care. 2005;28:2856-2863.

Brandle M, Zhou H, Smith BRK, Marriott D, Burke R, Tabaei BP, et al. The direct medical cost of type 2 diabetes. Diabetes Care. 2003;26:2300-2304.

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PROSIT Disease Modelling Community (Framework)

Contact details of main developer:

Wendelin Schramm, Heilbronn University [wendelin.schramm@hs-heilbronn.de]

Model website: https://www.prosit.de

Type of diabetes: Type 2 Diabetes

Brief Description:

Credibility and transparency of health-economic diabetes models is sometimes considered a problem. Therefore, the authors started in 2006 to develop open source models for the important medical complications of type 2 diabetes mellitus.

PROSIT is called by the authors a modelling framework as there is not a single diabetes model, but currently six diabetic complication models for Coronary Heart Disease, Stroke, Nephropathy, Retinopathy, Amputation, and Hypoglycaemia.

These are Markov models implemented as spreadsheet tables in OpenOffice.org and LibreOffice. All models are subject to a version control and old versions remain available online in order to assure the reproducibility of model calculations. They can be downloaded on the internet from the PROSIT Wiki.

The models are published online with a basic set of input data that can be easily changed according to the discretional choice of the user. The patient characteristics have been derived from the German ProValue study program. A cost data set for Germany was derived from the German KoDim-Study and reflects the year 2015. QALYs have been derived from the literature. The models allow the discounting of costs and effects. A separate validation toolkit allows the standardised validation by means of one-way sensitivity analysis of new model versions to allow comparison with previous models. The models due to their design do not support probabilistic sensitivity analysis.

The model framework is part of a higher education concept to link science with teaching. Thus, the core modellers are supported frequently by student contributions.

Funding source for development of model: The model development started with no funding whatsoever in 2006. In the time period 2010/2011 a non-restricted research grant from NovoNordisk, Denmark was received. Since 2015 the model development is supported by a research grant from Roche Diabetes Care Germany GmbH, Mannheim.

Key Publications:

Schramm W, Sailer F, Pobiruchin M, Weiss C. PROSIT Open Source Disease Models for Diabetes Mellitus. Stud Health Technol Inform. 2016;226:115-8. PMID: 27350481

Seitz P, Fendrich L, Hempe H, Rickmann J, Christophidis B, et al. Validierung des PROSIT CHD Type 2 Diabetes Herzinfarktmodells. Diabetologie und Stoffwechsel 2017; 12(S 01): S1-S84.

Scottish CVD Policy Model

Contact details of main developer:

Jim Lewsey, University of Glasgow [jim.lewsey@glasgow.ac.uk]
Francesco Manca, University of Glasgow [Francesco.Manca@glasgow.ac.uk]

Type of diabetes: Type 2 Diabetes

Brief Description:

This model was originally built as a cardiovascular disease policy model aimed to evaluate the impact of primary prevention interventions on life expectancy and quality adjusted life expectancy. The model is developed using data from a cohort study based on a Scottish Heart Health survey (SHHEC), linked to Scottish morbidity and death records. The covariates used in the modelling have been added to in order to take part in this challenge.

This model is a state transition model, where individuals are free of CVD at baseline and can transit to three CVD event states (two non-fatal and one fatal) and one non-CVD death state. Individuals who have a non-fatal first event are then followed up until death (or censoring). Under a competing risk approach, the hazards of first events are modelled using parametric survival analysis. Survival following a first non-fatal event is also modelled using parametric survival analysis. A key feature of the original model is including a variable that is an area-based measure of socioeconomic deprivation (SIMD) as a covariate. Including SIMD as an independent risk factor has a potential twofold effect: limiting omitted variable biases and taking into account for inequalities, which is crucial for policy purposes.

The cohort included SHHEC participants aged between 25 and 74 years without prior CVD events. The model requires specification of demographics and risk factors. Measures for diabetes and family history of heart disease were self-reported in the SHHEC survey.

The model provides different life expectancies between sexes and across diabetic and non-diabetic individuals. Compared to Scottish lifetables, the model over-estimates Lys and this can be partially explained by the fact that our population was chosen to be CVD-free at baseline.

The original model was assessed for discrimination, validation and calibration.

Funding source for development of model: The development of the policy model was funded by the Chief Scientist Office for Scotland (PI Prof Andy Briggs).

Key Publications:

JD Lewsey, et al. "A cardiovascular disease policy model that predicts life expectancy taking into account socioeconomic deprivation." Heart (2014): heartjnl-2014.

KD Lawson, et al. "A cardiovascular disease policy model: part 2—preparing for economic evaluation and to assess health inequalities." Open heart 3.1 (2016): e000140.

The Scottish Government. Summary Technical Report—summary report detailing the domains, indicators and methodology of SIMD 2004.

SHARP CKD-CVD Model

Contact details of main developer:

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Borislava Mihaylova, University of Oxford & Queen Mary University of London [boby.mihaylova@dph.ox.ac.uk]

Model website: http://dismod.ndph.ox.ac.uk/kidneymodel/app/

Type of diabetes: Type 1/ Type 2/ Gestational/ Pre-diabetes Moderate-to-advanced chronic kidney disease with 22% of people with type 1 & type 2 diabetes mellitus (exact type unknown)

Brief Description:

The SHARP CKD-CVD model is a long-term policy model in moderate-to-advanced chronic kidney disease (CKD) with focus on cardiovascular disease (CVD) morbidity. The model was developed using detailed patient-level data from the 9,270-participant Study of Heart and Renal Protection (SHARP) (mean follow-up of participants about 5 years; 22% of participants with diabetes at entry) and multivariate regression equations for disease risk, healthcare cost and quality of life. Information on the participants' sociodemographic characteristics (eg age, gender, ethnicity, BMI), disease risk factors (eg smoking, blood pressure, lipid profile) and prior morbidity (eg diabetes, vascular disease, albumin-to-creatinine ratio) at entry into SHARP as well as major within-trial events (cardiovascular events and annual CKD stage) were used to estimate individualised CKD and CVD risk equations. These were combined into a Markov model with an annual cycle allowing for the interdependence between CKD and cardiovascular complications and with transitions between CKD stages (3B, 4, 5, on dialysis, with kidney transplant) and cardiovascular events (major atherosclerotic events, haemorrhagic stroke, vascular death).

The model was validated internally in categories of participants in SHARP, as well as in three external CKD patient cohorts and against existing disease risk scores. It simulates long-term outcomes of patients with CKD (eg progression of CKD, experience of cardiovascular events and death, health-related quality of life and healthcare costs) and can also be used to evaluate the long-term comparative effectiveness and cost-effectiveness of interventions aimed at reduction of cardiovascular event risks (e.g. therapies targeting cholesterol or blood pressure).

The freely available web-based interface to the model allows the user to specify customised analytical scenarios including target patient or population groups, intervention and respective healthcare cost and quality of life factors.

Funding source for development of model: Merck & Co., Whitehouse Station, NJ USA; British Heart Foundation, UK Medical Research Council, Australian National Health Medical Research Council.

Key Publications:

Schlackow I, Kent S, Herrington W, Emberson J, Haynes R, Reith C, Wanner C, Fellström B, Gray A, Landray MJ, Baigent C, Mihaylova B; SHARP Collaborative Group. A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease. Heart. 2017 Dec;103(23):1880-1890.

Kent S, Schlackow I, Lozano-Kuehne J, Reith C, Emberson J, Haynes R, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrol. 2015;16(1):65.

SPHR CVD Prevention Model

Contact details of main developer:

Chloe Thomas, University of Sheffield [c.thomas@sheffield.ac.uk]

Type of diabetes: Type 1 & 2 Diabetes

Brief Description:

The SPHR CVD Prevention Model is an individual patient simulation model programmed in R. It was developed to evaluate the cost-effectiveness of a range of interventions aimed at detecting or managing six conditions that increase risk of cardiovascular disease (diabetes [type 1 and type 2], non-diabetic hyperglycaemia, chronic kidney disease (CKD), atrial fibrillation (AF), hypertension and high cholesterol/high cardiovascular risk including familial hypercholesterolaemia (FH). The model is an adaptation of the SPHR Diabetes Prevention Model. The model can be used to estimate the long-term costs saved, cardiovascular events prevented, and life years and QALYs gained for people with one or more of the CVD high risk conditions undergoing one or more of the detection or management interventions. The model uses the Health Survey for England 2014 as its baseline population.

The model combines data from a number of sources to describe risk factor trajectories and multiple complications and comorbidities relating to the CVD high risk conditions. BMI, systolic blood pressure, and cholesterol trajectories have been estimated based on longitudinal data from the Whitehall II study. These trajectories are used to define the development of diabetes, non-diabetic hyperglycaemia, hypertension and high cholesterol. HbA1c progresses linearly in people with type 1 diabetes. AF is modelled using Framingham risk equations, whilst CKD stages are modelled using a risk equation developed from Health Survey for England data. FH is assigned randomly to individuals with the highest cholesterol levels in each age group.

Cardiovascular events are estimated using the QRISK2 and QStroke risk scores to be representative of the UK population. A series of modifications have been applied to take account of the additional high risk conditions and interventions not included in the original algorithms. The risk of CVD is also assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS. Microvascular events in people with diabetes are estimated from the UKPDS2 outcomes model. Other outcomes include congestive heart failure, breast cancer, colorectal cancer, osteoarthritis, depression, dementia, major bleed, cardiovascular mortality, cancer mortality, bleed mortality and all-cause mortality. All health events incur costs and utility decrements.

Funding source for development of model:

Key Publications:

Thomas, C., Sadler, S., Breeze, P., Squires, H., Gillet, M. & Brennan, A. (2017) Assessing the potential return on investment of the proposed NHS Diabetes Prevention Programme in different population subgroups: an economic evaluation. BMJ Open. 7:e014953.

Breeze PR, Thomas C, Squires H, Brennan A, Greaves C, Diggle P, Brunner E, Tabak A, Preston L & Chilcott J (2017) Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK. Diabetic Medicine, 34(8), 1136-1144.

Breeze, P., Thomas, C., Squires, H., Brennan, A., Greaves, C., Diggle, P.J., Brunner, E., Tabak, A., Preston, L. & Chilcott, J. (2017) The impact of type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. Diabetic Medicine

SPHR Type 2 Diabetes Treatment Model

Contact details of main developer:

Dan Pollard, University of Sheffield [d.j.pollard@sheffield.ac.uk]

Type of diabetes: Type 2 Diabetes

Brief Description:

The SPHR Diabetes treatment model is an individual patient simulation model programmed in R. It was developed to evaluate the effect of treatments for people with type 2 diabetes in the United Kingdom. The model is an adaptation of the SPHR diabetes prevention model, which was designed to evaluate public health interventions to prevent diabetes and cardiovascular disease in the United Kingdom. The model can be used to estimate the long-term costs, life years and QALYs gained for people with diabetes.

The model combines data from a number of sources to describe longitudinal risk factor trajectories and multiple complications and comorbidities relating to diabetes. BMI, systolic blood pressure, Total and HDL cholesterol trajectories have been estimated based on longitudinal data from the Whitehall II study. These trajectories represent natural changes as people age and depend upon personal characteristics such as: gender, ethnicity and, smoking status.

A three-stage diabetes treatment regimen is applied in the model. At diagnosis all patients are prescribed metformin. If HbA1c increases above 8.48% the individual is prescribed the more expensive Gliptins in addition to Metformin and experience a treatment change related fall in their HbA1c. If their HbA1c increases above 9.5%, they are prescribed insulin and again experience a treatment change related fall in their HbA1c. Individuals receive opportunistic screening for hypertension and cardiovascular risk.

Microvascular, Macrovascular and mortality events are estimated using the UKPDS outcomes model v2 risk equations, so that the simulation is representative of a population with type 2 diabetes. Other outcomes include atrial fibrillation, micro/macroalbuminuria, breast cancer, colorectal cancer, osteoarthritis and depression. All health events incur costs and utility decrements.

The patient characteristics can be user specified for each decision problem. In previous analyses, the model has been used to analyse a UK based population. Consequently, most characteristics were obtained from NICE NG28, with other characteristics been sourced from UKPDS sources.

Funding source for development of model:

Key Publications:

Breeze PR, Thomas C, Squires H, Brennan A, Greaves C, Diggle P, Brunner E, Tabak A, Preston L & Chilcott J (2017) Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK. Diabetic Medicine, 34(8), 1136-1144.

Winkley K, Upsher R, Stahl D, Pollard D, Brennan A, Heller S, Ismail K. A systematic review of psychological interventions to improve motivation for self-management in people with type 1 and type 2 diabetes. Health Technology Assessment. Forthcoming

Treatment Transition Model (TTM)

Contact details of main developer:

Harry Smolen, Medical Decision Modeling Inc. [smolen@mdm-inc.com]

Type of diabetes: Type 2 Diabetes

Brief Description:

The MDM-TTM is an object-oriented C# simulation model which estimates clinical and economic outcomes for patients with T2DM under user-specified treatment strategies. The MDM-TTM is based on a sample of individual patients generated from baseline demographic (e.g., age, gender, ethnicity, and HbA1c level) and clinical characteristics (e.g., systolic blood pressure [SBP], total cholesterol, high-density lipoprotein [HDL] and low-density lipoprotein [LDL], body mass index [BMI]), and diabetic comorbidities (e.g., previous stroke). Each patient is simulated against two treatment strategies, each defined as an ordered collection of current and/or prospective anti-diabetic treatments. The MDM-TTM then estimates patient outcomes and costs associated with each strategy. To increase efficiency, population replications are parallelized.

The treatment model used within the MDM-TTM escalates patients to the next step of a strategy based on HbA1c. The MDM-TTM contains data for HbA1c efficacy, HbA1c drift, hypoglycaemia, and adherence for every user-specified class of T2DM treatment. It also allows users to create new treatments or variants of current treatments. Additionally, the treatment model within the MDM-TTM allows for users to model treatment effects beyond HbA1c such as changes to BMI and/or complication risks.

Based on the initial patient characteristics, the sequence of treatments, the timing of treatment escalation, and treatment clinical impacts, patient outcomes are estimated using the UKPDS 82 risk equations. These outcomes include kidney disease, blindness, lower extremity amputation, stroke, and coronary heart disease (myocardial infarction, ischemic heart disease, and congestive heart failure). Severe and non-severe hypoglycaemia events are estimated based on trial and real-world data. Health related quality of life (HRQoL) measures are also included in the model. Using treatment cost data and treatment use, pharmacy and direct complication costs (including hypoglycaemia) are estimated, The MDM-TTM also estimates costs associated with routine diabetic maintenance. MDM-TTM outputs include a large array of standard economic and clinical outcome outputs, graphical plots over time, and optional customized data.

Funding source for development of model: The model was developed primarily with MDM internal funding with initial funding form the U.S. National Institutes of Health – National Institute of Diabetes and Digestive and Kidney Diseases.

Key Publications:

Curtis BH, Curtis S, Murphy DR, **Gahn JC**, **Perk S**, **Smolen HJ**, Murray J, Numapau N, Bonner JS, Liu R, Johnson J, Glass LC. Evaluation of a patient self-directed mealtime insulin titration algorithm: a US payer perspective. J Med Econ. 2016 Jun;19(6):549-56. Epub 2016 Feb 1. PubMed PMID: 26756804.

Smolen HJ, Murphy DR, Gahn JC, Yu X, Curtis BH. The evaluation of clinical and cost outcomes associated with earlier initiation of insulin in patients with type 2 diabetes mellitus. J Manag Care Spec Pharm. 2014 Sep;20(9):968-84. PubMed PMID: 25166296.

S Perk, DR Murphy, JC Gahn, X Yu, and HJ Smolen. Estimating clinical and economic outcomes following a diabetes-related vascular complication. Value in Health. May 2015. Volume 18, Issue 3, Pages A59–A60.

HJ Smolen and X Yu. Using a treatment transition model to evaluate the effects of neglecting Hba1c drift in oral anti-diabetic drugs for type 2 diabetes. Value in Health. May 2015Volume 18, Issue 3, Page A53.

UKPDS Outcomes Model

Contact details of main developer:

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Model website: https://www.dtu.ox.ac.uk/outcomesmodel/

Type of diabetes: Type 2 Diabetes

Brief Description:

The UKPDS Outcomes Model (UKPDS-OM) is based on patient-level data from the United Kingdom Prospective Diabetes Study (UKPDS). It simulates type 2 diabetic populations modelling the occurrence of eight diabetes-related complications (MI, ischaemic heart disease, stroke, heart failure, amputation, renal failure, diabetic ulcer and blindness in one eye), second events (MI, stroke, and amputation) and death to estimate quality-adjusted life expectancy, life expectancy, and costs. In brief, the UKPDS-OM is based on an integrated system of parametric equations that predict the annual probability of any of the above complications and Monte Carlo methods to predict the occurrence of events. The likelihood of the events is based on patient demographics, duration of diabetes, risk factor levels, and history of diabetes-related complications. Different treatment and management strategies are evaluated through their impact on risk factor levels. A key aspect of the model is its ability to capture the clustering or interaction of different types of complications at the individual patient level. The model is a probabilistic discrete-time multi-state model. Patients start with a given health status (e.g., age, sex, duration of diabetes, risk factor values, and no complications) and can have one or more nonfatal complications and/or die in any model cycle. When a patient experiences a complication, their utility is permanently decremented such that they accumulate quality-adjusted life-years at a slower rate. Utility decrements and costs associated with events are estimated from the same patient-level data set. Elements of the UKPDS Outcomes Model have been widely used in many other prediabetes and diabetes simulation models.

Funding source for development of model: UKPDS OM version 2 was funded by Australian National Health and Medical Research Council grants (no. 512463 and no. 571372) and a UK Medical Research Council grant (ID: 87386).

Key Publications:

Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic Medicine 2015;32:459-466

Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ 2014; 23(4):487-500.

Leal J, Hayes AJ, Gray AM, Holman RR, Clarke PM. Temporal Validation of the UKPDS Outcomes Model Using 10-Year Post trial Monitoring Data. Diabetes Care 2013;36:1541-1546

Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925-1933.

Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, Matthews DR, Stratton IM, Holman RR. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS 68). Diabetologia 2004;47:1747-1759.