Economics Modelling and Diabetes: The Mount Hood 2016 Challenge

Kantonsspital of St. Gallen

St. Gallen, Switzerland

16th – 18th September 2016

Contents

Economics, Modelling and Diabetes:

The Mount Hood Challenge, St. Gallen 2016

Conference Centre Map and General Information

Location: The conference will be held at the Kantonsspital of St. Gallen, Rorschacher Strasse 95, 9007 St. Gallen.

Registration for the optional pre-conference workshop will commence at 12.30pm on Friday, 16th September.

Registration for the conference will be from 8.30am onwards on Saturday, 17th September. The conference will conclude at 3.15pm Sunday, 18th September 2016.

Conference registration includes lunches/refreshments and a conference dinner on the evening of 17th September.

Mount Hood Organising Committee 2016

Philip Clarke, The University of Melbourne

Jose Leal, The University of Oxford

Phil McEwan, Health Economics and Outcomes Research Ltd

Andrew Palmer, Menzies Institute, University of Tasmania

Michael Willis, The Swedish Institute for Health Economics

Michelle Tew, University of Melbourne

The organising committee is chaired by Professor Philip Clarke, University of Melbourne and this year's conference is being hosted by Michael Brändle of Kantonsspital St. Gallen.

Thanks are due to:

Michael Brändle and Ruth Perlt-Vögeli for local organising; Nick Woods for assistance with developing the website; Jose Leal, Christian Asseburg and Mike Willis on developing the Challenges; Xinyang Hua and Michelle Tew for working on the program.

List of Participants

Donna	Ashley	Novo Nordisk
Christian	Asseburg	IHE The Swedish Institute for Health Economics
Jay	Bae	Eli Lilly and Company
Jacob	Barhak	-
Klas	Bergenheim	AstraZeneca
Michael	Brändle	Kantonsspital St. Gallen
Penny	Breeze	University of Sheffield
Alan	Brennan	University of Sheffield
Philip	Clarke	University of Melbourne
Helen	Dakin	University of Oxford
Talitha	Feenstra	RIVM/UMCG
Volker	Foos	IMS Health
John	Forbes	University of Limerick
Kurt	Fortwaengler	Roche Diabetes Care GmbH
James C	Gahn	Medical Decision Modeling Inc.
Michael	Gains	IMS Health
Divina	Glah	Novo Nordisk
Jason	Gordon	Health Economics and Outcomes Research Ltd
Alastair	Gray	University of Oxford
Jens	Gundgaard	Novo Nordisk A/S
William	Herman	University of Michigan
Thomas	Hoerger	RTI International
Xinyang	Hua	University of Melbourne
Deanna	Isaman	University of Michigan
Pierre	Johansen	IHE The Swedish Institute for Health Economics
Josh	Knight	University of Melbourne
Shihchen	Kuo	University of Michigan
Neda	Laiteerapong	University of Chicago
Mark	Lamotte	IMS Health Consulting

List of Participants (continued)

Jose	Leal	University of Oxford
Philip	McEwan	Health Economics and Outcomes Research Ltd
Balazs	Nagy	SYREON Ltd.
Bertalan	Nemeth	SYREON Ltd.
Cheryl	Neslusan	Janssen
Patrick	O'Connor	HealthPartners Institute
Katherine	Ogurtsova	Deutsches Diabetes-Zentrum (DDZ)
Andrew	Palmer	University of Tasmania
Dan	Pollard	University of Sheffield
Richard	Pollock	Ossian Health Economics and Communications GmbH
Lei	Qin	AstraZeneca
Samantha	Roberts	University of Oxford
Katrin	Schimke	Kantonsspital SG
Katharina	Schremser	Helmholtz Zentrum München GmbH – German Research Center For Environmental Health
Lei	Si	Menzies Institute for Medical Research
Annabelle	Slingerland	Institute of Public Health
Joel	Smith	University of Oxford
Harry J	Smolen	Medical Decision Modeling Inc.
Oleh	Syarkevych	JSC Farmak
Laszlo	Szilberhorn	SYREON Research Institute Ltd.
Shana	Traina	Janssen
An	Tran Duy	University of Melbourne
Christina	Tzogiou	ZHAW School of Management and Law
William	Valentine	Ossian
Kate	Van Brunt	Eli Lilly & Company
Zoltan	Voko	SYREON Ltd.
Michael	Willis	IHE The Swedish Institute for Health Economics
Josan	Yauw	UMC Utrecht

Pre-conference workshop
Diabetes simulation modelling through the looking glass

16 September 2016 1pm-5pm

Building 8, 2nd Floor (see map)

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.

Professor Andrew Palmer was a 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, Modelling and Diabetes:
Mount Hood 8 Challenge 2016

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 seven previous diabetes simulation modelling conferences that have been held since 1999.

The theme of the 2016 Challenge will be how to improve the transparency of simulation models. It will feature both challenges and debates on how this can best be achieved. The conference will also focus on how best to convey information on health outcomes to clinicians and patients.

Speakers will include:

- **Rod Jackson**, University of Auckland, contributing a long history in developing tools to explain cardiovascular risk.
- **Amanda Adler**, Addenbrooke's Hospital (Cambridge) chair of NICEs Technology Appraisal committee.
- **Barrie Chubb,** Regional Health Economics Manager, Novo Nordisk.

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

Economics, Modelling and Diabetes: Mount Hood 8 Challenge 2016

Guest Speakers

Professor Rod Jackson

Rod Jackson is a professor of epidemiology at the University of Auckland, New Zealand. He is medically trained, has a PhD in epidemiology and is a fellow of the New Zealand College of Public Health Medicine.

He has 35 years of research experience in cardiovascular disease epidemiology. In the 1990s he led the development of New Zealand's absolute risk-based clinical guidelines for managing CVD risk factors. For the past 15 years his research has been mainly focused on CVD risk prediction and its application in clinical practice. He leads a 'big-health data' research programme that generates very large cohort studies from web-based clinical decision support systems linked to national health databases to implement, monitor and improve CVD risk assessment and management in primary and secondary care. He has published over 270 papers in peer-reviewed journals.

Amanda Ingham Adler

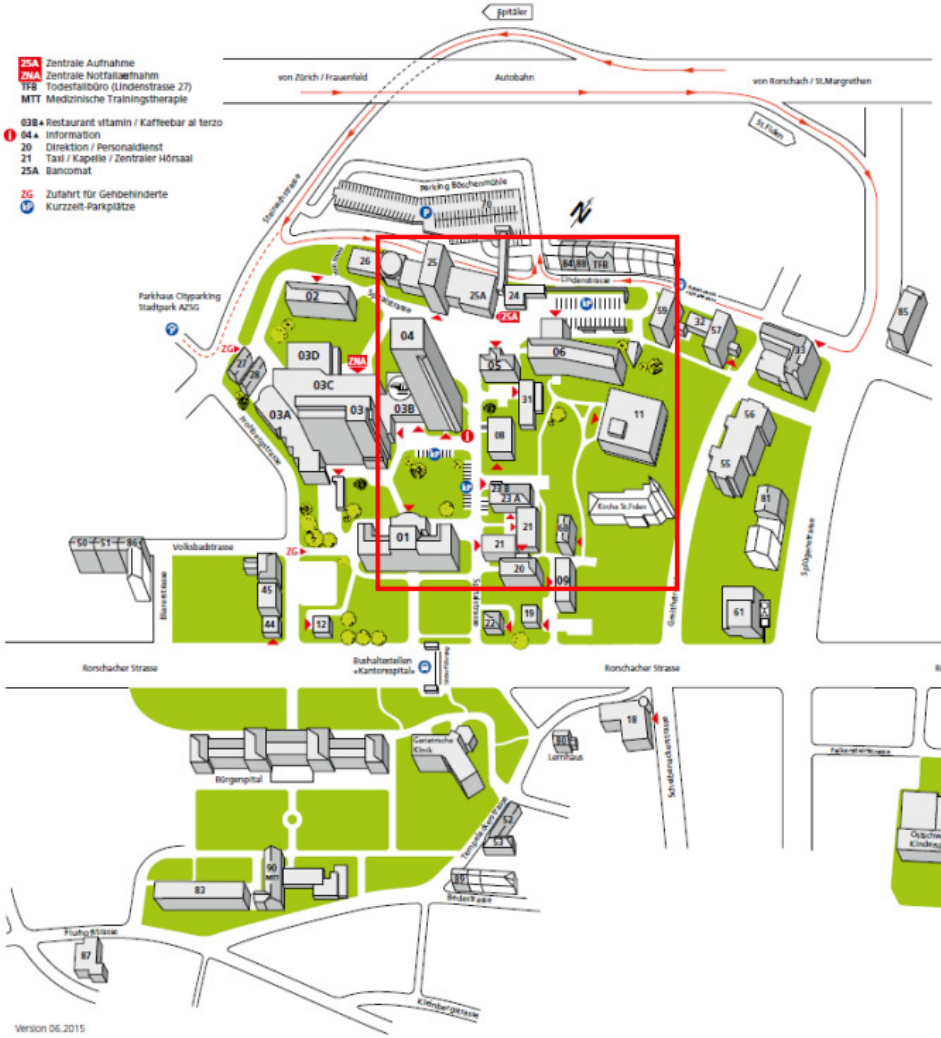
Amanda Ingham Adler trained in economics, medicine and epidemiology. She chairs a multi-disciplinary Technology Appraisal Committee at the National Institute for Health Excellence (NICE) and is a consultant physician at Addenbrooke's Hospital, Cambridge. Her clinical work involves patients' in-hospital, in out-patient clinics, and in the community. She holds an honorary position with the MRC Epidemiology Unit, Institute of Metabolic Sciences, Cambridge University.

Barrie Chubb

Barrie Chubb undertook his health economic training at City University in 2006, and has since worked as a health economist for Novo Nordisk.

In his time there Barrie has been involved in a number of submissions to all of the UK HTA authorities (NICE, SMC and AWMSG) as well as the NCPE in Ireland for diabetes therapies. Barrie's current role is that of 'Regional Health Economics Manager', in the European Health Economics and Outcomes Research team.

Areal Kantonsspital St.Gallen



25A Zentrale Aufnahme
ZNA Zentrale Notfallaufnahm
TFB Todesfallbüro (Lindenstrasse 27)
MTT Medizinische Trainingstherapie

03B Restaurant vitamin / Kaffeebar al terzo
04 Information
20 Direktion / Personaldienst
21 Taxi / Kapelle / Zentraler Hörsaal
25A Bancomat

ZG Zufahrt für Gehbehinderte
Kurzzeit-Parkplätze

Standort St.Gallen

Parkplatzsituation Kantonsspital St.Gallen
Ideal ist die Anreise mit dem öffentlichen Verkehr.Die Anzahl Parkplätze auf dem Areal des Kantonsspitals St.Gallen ist beschränkt.

Auf dem Areal stehen kostenpflichtige Kurzzeit-Parkplätze zur Verfügung.

Auf dem Parkdeck Böschenmühle, angrenzend an das Spitalareal, gibt es weitere Parkplätze. Zudem stehen Parkplätze im nahegelegenen öffentlichen Parkhaus Cityparking des Athletik-Zentrums zur Verfügung.

Weitere Informationen
071 494 11 11 oder www.kssg.ch

Öffentliche Verkehrsmittel

Stadtbus VBSG
Die Stadtbusse halten an der Rorschacherstrasse beim Kantonsspital St.Gallen (Haltestelle Kantonsspital) und an der Lindenstrasse (Haltestelle Spitalstrasse).

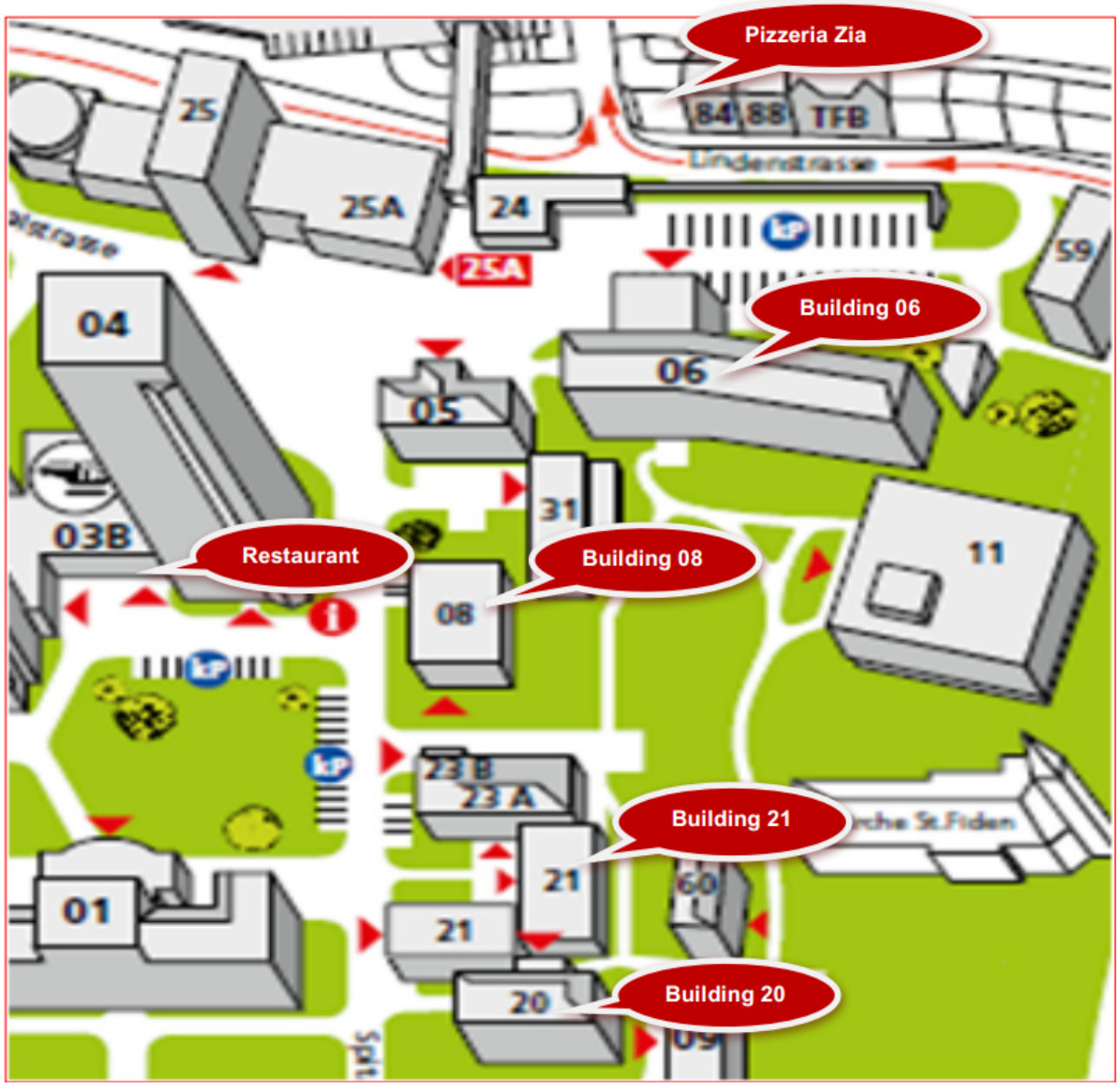
Linie 1	(Stephanshorn)
Linie 4	(Guggeien)
Linie 7	(Achslen)
Linie 11	(Mörschwil)
Linie 10	(Abacus-Platz)

Postauto
Die Postautokurse von und nach Rehetobel/Heiden, Eggersriet/Heiden und Goldach-Rorschach/Rorschacherberg, Tübach und Engelburg halten an der Haltestelle Kantonsspital.

Bahn
Ab Bahnhof St.Gallen-St.Fiden ist der Fussweg mit Schildern: «Spitäler/Kantonsspital» gekennzeichnet.

Auto
Über die Autobahnausfahrt «St.Fiden/Spitäler» oder via Innenstadt über die Steinachstrasse.

Kantonsspital St.Gallen



Building 21 – Lecture Hall
- Registration
- Plenary sessions
- Workshop
- Breaks
- Lunches

Building 06 / 4th floor
- Workshop

Building 20 / 1st floor
- Workshop

Building 08 / 2nd floor
- Optional Workshop : A Master Class in Diabetes Stimulation Modelling

Conference Program

Day 1	Saturday 17th September 2016		
8:30-9:00am	**REGISTRATION**		
9:00-9:10am	**Welcome –** Prof Philip Clarke, University of Melbourne Location**:** Building 21- Lecture Hall		
9:10-11:00am	**Mt Hood 2016: Transparency Challenge** Chair: Mike Willis, Institute of Health Economics, Lund Sweden Overview: Outline of the challenge & results --- Groups presenting a (very brief) overview of their model & how they would make their simulations transparent (5 Minutes per model) Cardiff Model ECHO-T2DM IMS CORE Diabetes Modelling Group Medical Decision Modelling (MDM) MICADO Michigan Model for Diabetes MMUs Diabetes Model SPHR Diabetes The Reference Model UKPDS Outcomes Model		
11:00-11:30am	***Tea and Coffee***		
11:30am-12:30pm	**General discussion of Validation Results** Chair: Alastair Gray, University of Oxford Location: Building 21 Lecture Hall		
12:30-1:30 pm	***Lunch***		
1:30-3:00pm	**Conference session 1** Lecture Hall (20 Minutes each)	**Conference session 2** Building 06 4th Floor (20 Minutes each)	**Conference session 3** Building 20 1st floor (20 Minutes each)
3:00-3:30pm	***Tea and Coffee***		
3:30-5:00pm	**Conference session 4** Lecture Hall (20 Minutes each)	**Conference session 5** Building 06 4th Floor (20 Minutes each)	**Conference session 6** Building 20 1st floor (20 Minutes each)
5:00- 6:00pm	**Business meeting: Where to next with Mt Hood?** Chair: Prof Philip Clarke Location: Building 21 Lecture Hall		
7:00pm onwards	**CONFERENCE DINNER Restaurant Falkenburg** (http://www.falkenburgsg.ch)		

Day 2	Sunday 18th September 2016
9:20-11:00am	**Challenge 2: What can we learn from Outcome tables** Cardiff Model ECHO-T2DM IMS CORE Diabetes Modelling Group MDM – TTM MICADO Michigan Model for Diabetes MMUs Diabetes Model SPHR Diabetes The Reference Model UKPDS Outcomes Model Chair: Philip Clarke Location: Building 21 Lecture Hall
11:00-11:30am	***Tea and Coffee Break***
11:30am-12:30	**Making the results of models understandable to clinicians and the patients** Plenary Speaker: Prof Rod Jackson, University of Auckland Chair: Amanda Adler, NICE.
12:30-1:30pm	***Lunch***
1:30-2:30pm	**Special Session: Creating new diabetes models** Chair: Neda Laiteerapong, University of Chicago Speakers: Philip Clarke- Type 1 models William Valentine - Type 1 models Josh Knight – CVD models Xinyang Hua – Calibrating CVD risk in an indigenous population
2:30-3:00pm	**What have we learned – general discussion**
3:00-3:15pm	***Wrap up- CLOSE (Afternoon Coffee to finish)***

Conference Sessions

(Based on submitted abstracts)

nstructions for presenters in conference sessions

- All presenters will have around 20 minutes each (including 5 minutes questions).
- A laptop computer and projector will be provided for your presentation, using Microsoft PowerPoint software.
- The time allocated for presentation will be 15 minutes. Allow a minimum of one minute per slide, preferably 2–3 minutes.
- Arrive at the meeting room before the session begins and contact the session convener for last-minute instructions or changes in the schedule.
- 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 17 September 2016 - 1:30-3:00pm

Presenter	Authors	Title	Location (Chair)
Jose Leal	Jose Leal, Peter Eibich, Alastair M Gray, Rury Holman, Alison J Hayes, Philip M Clarke	Life-expectancy and costs for people with type 2 diabetes	Building 21 Lecture Hall (Andrew Palmer)
Harry Smolen	JC Gahn, X Yu, S Perk, DR Murphy, and HJ Smolen	Estimating the cost effectiveness of a patient-directed mealtime insulin titration algorithm	
Patrick J. O'Connor	Patrick J. O'Connor, Todd P. Gilmer, JoAnn M. Sperl-Hillen, Heidi L. Ekstrom, A. Lauren Crain	Impact of Improving Diabetes Care on Quality Adjusted Life Expectancy (QALE) and Costs: A 30-Year Perspective	
Neda Laiteerapong	Neda Laiteerapong, Jennifer M. Cooper, Rochelle N. Naylor, Elbert S. Huang	Cost-effectiveness of Individualizing Glycemic Goals for U.S. Adults with Type 2 Diabetes	
Annabelle S. Slingerland	Slingerland AS, Choudhurry R, Redekop WK, Niessen LW	Follow up on the 6th Mount Hood Conference: filling the gap to model type 1 diabetes.	Building 06-4th Floor (Talitha Feenstra)
Dan Pollard	Daniel Pollard, Alan Brennan, Jackie Elliott	The estimation of post-treatment HbA1c using a beta regression in the Sheffield Type 1 Diabetes Policy Model.	
Oleh Syarkevych	Olha Zalis'ka, Oresta Piniazhko, Danylo Halytsky Lviv, Oleh Syarkevych	Cost analysis of insulin treatment regimens for patients with type 1 diabetes in the Ukrainian setting	
William Valentine	Pollock RF, Brändle M and Valentine WJ	A Covaried, Target-Based, Patient-Level Model of HbA1c Progression in Type 1 Diabetes	
An Tran-Duy	An Tran-Duy, Philip Clarke	Data structures and algorithms for modelling conditionally random events in a probabilistic discrete-time simulation model for type 2 diabetes: exploitation of modern C++ features	Building 20- 1st Floor (Alatasir Gray)
Helen A. Dakin	Helen A. Dakin, Rury R. Holman, José Leal, Alastair M. Gray	Combining parameter and sampling uncertainties within diabetes clinical outcome simulation models	
Phil McEwan	Phil McEwan, Volker Foos, Mark Lamotte	Replacing input probability distributions with mean values can bias simulation output: an illustration using the CORE diabetes model.	
Volker Foos	Volker Foos, Phil McEwan, Mark Lamotte	Implications of introducing patient heterogeneity in cost effectiveness modeling	

Saturday 17 September 2016 - 3:30-5:00pm

Presenter	Authors	Title	Location (Chair)
Balazs Nagy	A Zsólyom, L Szilberhorn, B Németh, B Nagy, Z Vokó	Impact of adjusting diabetes treatment pathways according to disease severity – the case of HbA1c and macular oedema	Building 21 Lecture Hall (Patrick O'Connor)
Joel Smith	Joel Smith, John Forbes	Breaking away from central tendencies: Using more flexible and informative economic models of the cost of healthcare for people with type 2 diabetes	
Michael Willis	Michael Willis, Christian Asseburg, Cheryl Neslusan, Andreas Nilsson	The Importance of HbA1c Evolution in Modeling Type 2 Diabetes Mellitus	
Pierre Johansen	Pierre Johansen, Michael Willis, Andreas Nilsson, Christian Asseburg, Cheryl Neslusan,	The Importance of Capturing Cardiovascular Benefits Not Mediated by Traditional Risk Factors in Type 2 Diabetes Mellitus (T2DM) Modeling	
Xinyang Hua	Xinyang Hua, Thomas Wai-Chun Lung, Andrew Palmer, Lei Si, William H. Herman, Philip Clarke	How consistent is the relationship between improved glucose control and modelled health outcomes for people with type 2 diabetes? A systematic review	Building 06-4th Floor (Neda Laiteerapong)
Jose Leal	Jose Leal, Talitha Feenstra, Eva Pagano	Challenges and opportunities for decision modelling from the onset of pre-diabetes onwards	
Josan S Yauw	Josan S Yauw, Joline W Beulens, Fariza Badloe, Linda M Peelen, Giel Nijpels, Amber A van der Heijden	Prediction models for the risk of retinopathy in persons with type 2 diabetes. A systematic review	
Christian Asseburg	Christian Asseburg, Michael Willis, Cheryl Neslusan, Agata Schubert	The Importance of Considering Differences in Network Meta-analyses (NMAs): An Example of Sodium Glucose Co-transporter 2 Inhibitors (SGLT2i)	
Alastair Gray	Alastair Gray, Oliver Rivero-Arias, Shelby D Reed, Yanhong Li, Rury Holman, Jose Leal	Can delaying onset of diabetes be cost-effective? A simulation study based on NAVIGATOR data	Building 20- 1st Floor (Alan Brennan)
Christina Tzogioua	Simon Wiesera , Christina Tzogioua, Sascha Hessa, Klaus Eichlera, Marie Azoulayb, Sima Djalalic, Thomas Rosemannc, Michael Brändled	Costs of hypoglycemia in insulin-treated diabetes in Switzerland: a health-economic analysis	
Melat Mamo	Melat Mamo, Meaza Demissie	Self-care practice and its associated factors among diabetic patients in Addis Ababa public hospitals, cross sectional study	
Josh Knight	Knight J Clarke P Jackson R	Do Seasons in Simulations matter? Should Modellers Take the Time of Year Into Account	

Mount Hood 2016 Challenges

Challenge #1: Transparency

Motivation

How reproducible are published simulation modelling studies? What is the best way to describe a simulation so that it can be reproduced? For this challenge we have selected two published papers. The purpose of this challenge is to determine how easy it is to reproduce the simulations undertaken in these studies. Beyond the level of agreement, the main point of this challenge assist in the development of checklist for documenting simulations. The ultimate purpose is to develop reporting guidelines that Mt Hood would publish collectively.

Instructions

1. The replication transparency challenge consists of attempting to replicate two studies: the UKPDS 72 and Baxter et al. 2016.
   - P. M. Clarke, A. M. Gray, A. Briggs, R. J. Stevens, D. R. Matthews, R. R. Holman, on behalf of the UK Prospective Diabetes Study (UKPDS) Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72) Diabetologia, May 2005, Volume 48, Issue 5, pp 868-877 (can be downloaded from: http://link.springer.com/article/10.1007%2Fs00125-005-1717-3)
   - M. Baxter, R. Hudson, J. Mahon, C. Bartlett, Y. Samyshkin, D. Alexiou andN. Hex Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit, Diabetes Medicines, Online: 15 APR 2016: DOI: 10.1111/dme.13062

2. For each of the published cost-effectiveness applications, please read the study publications carefully and carry out the following:
   a. Extract the information and load model to the best of your ability and judgment.
      i. If anything is contradictory or unclear, you decide, but document it (naming this Section 1 in your documentation).
   b. Document gaps (call this Section 2 in your documentation).
   c. Continue loading model using complementary sources.
      i. First, use other publications from the same study (for example, other UKPDS in the case of UKPDS 72).
      ii. It may be necessary to obtain inputs from other sources if they are not reported, or to convert inputs to other units etc.
      iii. Document fully the sources of all your inputs and any assumptions that were required, and document any gaps of necessary information. Note whether the missing information relates to differences in model design.

d. If your group published the study in question, try to replicate the analysis using only publically available information, and not any proprietary or other information available to you!

3. Simulate the same decision problems using your model. Note that UKPDS 72 includes three separate analyses: (i) blood glucose control with metformin in overweight patients; (ii) intensive blood glucose control; (iii) tighter blood pressure control. Please focus only on intensive blood glucose control. If you have time, you can try to replicate the other interventions. For the Baxter paper, there are separate analyses for T1DM and T2DM. Please focus on T2DM, but feel free to simulate T1DM as well.

4. *Result extraction:* Extract the relevant results from your simulations into the provided Excel file for capturing outcomes.

5. *Documenting your methods:* Prepare two summaries describing the simulations you have undertaken:
   - A brief summary (less than 300 words) that could potentially form the methods section of a published paper
   - A detailed methods section that you believe would document the simulation you have undertaken so that it is fully transparent (for a working definition of transparent, assume that you describe your model in sufficient details that would enable an informed but "blinded" researcher (i.e. a researcher not having access to simulated results) to reproduce your results.

6. Prior to the meeting:
   a. Submit the result Excel file ("Challenge 1 Results Reporting Template.xls").
   b. Submit the documentation (Sections 1 and 2), being sure to include a summary of what you think are the gaps in the existing methods contained in the published studies
   c. Submit the two methods sections of how you would document your simulations

7. Deadline: Please submit the results by September 4th, 2016.

Challenge #2: Communicating Outcomes

Background

A few years ago the UKPDS Outcomes model was used to produce some Life Expectancy tables (Jose Leal, Alastair M. Gray, Philip M. Clarke, Development of life-expectancy tables for people with type 2 diabetes. European Heart Journal, Volume 30, Issue 7, 2009. http://eurheartj.oxfordjournals.org/content/30/7/834).

The purpose of this challenge is two-fold. The first is for modelling groups to produce comparable outcome tables using their own models for people with Type 2. These tables are a method for communicating outcomes to clinicians and patients. They are also intended to promote transparency as they enable comparisons of models across a broad range of standardized simulations, i.e. a standard set of simulations for patients with a wide variation in characteristics would allow users to understand what risk factors drive variations in model outcomes.

Instructions

1. Attached, please see a PDF "Development of Life-Expectancy Tables" that contains a table-based analysis that presents (life expectancy over a range of covariate values at baseline) for a typical patient or cohort.

2. Using the attached input values (Excel file "Challenge 2 Input Sheet.xlsx"), replicate this analysis using your model.
    a. Switch off discounting. Life-time time horizon (or longest time-frame possible).
    b. Set up a simulation matching all inputs in the specified Excel sheet. Note following the UKPDS study, please assume that all risk factor values remain constant.
    c. Please use public data from the characteristics of the UKDPS population (e.g. as reported in UKPDS 33), or make plausible assumptions regarding any other risk factor values.
    d. For the covariates (or inputs) that are being varied in the table-based analysis, set up and run your model such that the patient baseline inputs are varied accordingly.
    e. Throughout, hold the risk factors constant through life-time (as in the Excel file).

f. Where your model requires different data or data in a different format, document your assumptions, but try to match the instructions as closely as possible.
g. If anything is contradictory or unclear, you decide, but fully document it.

3. Simulate and extract life expectancy, lifetime QALYs (undiscounted) and, if possible, rates of MI, Stroke, CHF, Overall CVD, ESRD, and Amputation.

4. Standard set of tables for reporting results will be circulated to groups registering for the challenge.

5. Prior to the meeting:
    a. Submit the result output capture file which will match that produced in the EHJ to mthood2016@gmail.com.
    b. Submit documentation: The inputs and assumptions required, any gaps in information

6. Deadline: Please submit the results by September 4th, 2016.

Models Participating in Challenges

- **Cardiff Model**
- **ECHO-T2DM**
- **IMS CORE Diabetes Model**
- **Medical Decision Modeling (MDM) – Treatment Transitions Model (TTM)**
- **MICADO**
- **Michigan Model for Diabetes**
- **MMUs Diabetes Model**
- **SPHR Diabetes**
- **The Reference Model**
- **UKPDS Outcomes Model**

Cardiff Model

Lead Presenter: Phil McEwan

Other team members attending: Jason Gordon

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 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.

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;13:12. doi: 10.1186/s12962-015-0038-8.

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;22(1):121.

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. 2016. Accepted for publication. PlosOne.

ECHO-T2DM

Lead Presenter: Michael Willis

Other team members attending: Christian Asseburg and Pierre Johansen

Brief Description:

ECHO-T2DM is a stochastic, 2nd order, 'multi-application' microsimulation cost-effectiveness model of treatment intervention in T2DM with Markov health states that reflect different severities of kidney disease, neuropathy, and retinopathy, four types of macrovascular disease, and mortality. The model is programmed in R with Microsoft Excel® interface.

ECHO-T2DM generates parameter values (e.g., treatment effects, unit costs, and risk equation coefficients, and AE rates) for *i* cohorts drawn from user-defined probability distributions and generates initial patient characteristics including demographics (e.g., age, sex, ethnicity), clinical (e.g., T2DM duration, HbA1c, SBP, BMI, eGFR, serum cholesterol, pulse pressure (PP), ACR, WBC, heart rate, and smoking status), and pre-existing micro- and macrovascular complications (e.g., microalbuminuria, ESRD, symptomatic neuropathy, MI, and stroke) for *j* hypothetical patients in each cohort. Correlation between the initial characteristics is used to account for observed patterns of risk factor clustering.

The user can choose between four sets of macrovascular risk equations, including UKPDS 68, UKPDS 82, ADVANCE, and the Swedish NDR, and two sets of mortality risk equations (UKPDS 68 and 82). A fully-integrated sub-model of chronic kidney disease (CKD) based on the CDC Model of CKD is implemented in ECHO-T2DM.

For the economic comparison, the user defines anti-hyperglycemic treatment sequences (a sequence starting with the new intervention vs. up to ten comparator sequences, such as current care); in addition, the user can define treatment sequences for hypertension, dyslipidemia, and obesity. The cycle length is one year and the time horizon is user-definable.

Key Publications:

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. Forthcoming in Journal of Population Therapeutics and Clinical Pharmacology

Neslusan C, Teschemaker A, Johansen P, Willis M, Valencia-Mendoza A and Puig A. Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metforminin Patients with Type2 Diabetes Mellitus in Mexico. Value in Health Regional Issues 2015; 8C: 8-19. Published Online: June 03, 2015. http://dx.doi.org/10.1016/j.vhri.2015.01.002

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

IMS CORE Diabetes Model

Lead Presenter: Volker Foos

Other team members attending: Mark Lamotte, Phil McEwan

Brief Description:

The IMS-CORE-Diabetes-Model is a no-product specific, diabetes policy analysis tool that performs real time simulations. Disease progression 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. Analyses, including first and second order Monte Carlo simulations 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 s it becomes available. The creation of country-, health maintenance organization- or provider specific versions of the model is possible. Noteworthy, recent updates to the model include a detailed hypoglycaemia sub-module, the inclusion of alternative sets of contemporary risk equations including equations from the UKPDS82, the Swedish-National-Diabetes-Register, the ADVANCE-risk-engine, the Fremantle-study and others. Moreover the type-1-section of the model was entirely revisited to incorporate 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.

Key Publications:

McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. Value Health. 2014 Sep; 17(6):714-24.

Davies MJ1, Chubb BD, Smith IC, Valentine WJ. Cost-utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus.Diabet Med. 2012 Mar;29(3):313-20.

Vivian A. Fonseca, Hayden Smith, Nitesh Kuhadiya, Sharice M. Leger, C. Lillian Yau, Kristi Reynolds, PHD, Lizheng Shi, Roberta H. McDuffie, Tina Thethi, and Jennifer John-Kalarickal. Impact of a Natural Disaster on Diabetes: Exacerbation of disparities and long-term consequences. Diabetes Care. 2009 Sep; 32(9): 1632–1638.

Palmer AJ1, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA. The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin. 2004 Aug;20 Suppl 1:S5-26.

Palmer AJ1, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin. 2004 Aug;20 Suppl 1:S27-40.

Medical Decision Modeling (MDM) – Treatment Transitions Model (TTM)

Lead Presenter: Harry J. Smolen

Other team members attending: James G. Gahn

Brief Description:

The Treatment Transitions Model (TTM) is a Monte Carlo microsimulation model which estimates clinical and economic outcomes for patients with type 2 diabetes mellitus (T2DM) under user-specified treatment paradigms. The TTM simulation begins with creating an individual simulated patient with baseline demographic and clinical characteristics. The baseline characteristics include age, gender, ethnicity, and HbA1c. Clinical characteristics include systolic blood pressure, total cholesterol, high-density (HDL) and low-density lipoprotein (LDL), body mass index (BMI), and estimated glomerular filtration rate (eGFR). Comorbidities estimated from the TTM include nephropathy, neuropathy, retinopathy, stroke, and coronary heart disease.

Based on the comorbidity-related mortality and overall natural mortality, the patient's mortality is estimated. Treatment escalation within TTM is primarily controlled by increases to HbA1c and the sequence of treatments being evaluated. Patients not achieving durable control of their HbA1c are typically subject to drift after a period of time on a specific treatment (a treatment modifiable input). Once a patient's HbA1c fails to decline or remain below the target for a prescribed amount of time (treatment specific), the patient will advance to the next step in their treatment progression. The model user can select the specific treatment progression (i.e., series of treatments) to be evaluated.

In the TTM, event and continuing medical costs are estimated along with pharmacy costs. The TTM also includes estimation of medical costs associated with hypoglycaemic events.

Key Publications:

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.

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. doi: 10.3111/13696998.2016.1141098. Epub 2016 Feb 1. PubMed PMID: 26756804.

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.

MICADO: Modelling Integrated Care for Diabetes based on Observational data

Lead Presenter: Talitha Feenstra

Other team members attending: Josan Yauw

Brief Description:

Simulation models can assist in comparing the cost-effectiveness of interventions. Most models concentrate on existing diabetes patients. However, the MICADO model was developed for the evaluation of long term cost-effectiveness of interventions in both diabetes patients and the general population. Its basic structure is that of a dynamic population model, with either overlapping birth-cohorts or a cohort of diabetes patients being followed over annual time cycles. MICADO is a Markov-type, multistate transition model linking risk factors to incidence of diabetes and to micro- and macrovascular complications. Being based on GP registry data, as well as other population-wide data sources, it contains a mixed diabetes population of mainly type 2. Microvascular complications modelled are diabetic foot, nephropathy and retinopathy, macrovascular complications modelled are AMI, other CHD, CVA, and CHF. Outcomes are prevalence of complications, and quality of life. Costs are being added. Parameter uncertainty analysis can be performed concerning estimated disease/complication prevalence and treatment effectiveness parameters.

Key Publications:

A. A. W. A. van der Heijden, T. L. Feenstra, R. T. Hoogenveen, L. W. Niessen, M. C. de Bruijne, J. M. Dekker, C. A. Baan and G. Nijpels. “Policy evaluation in diabetes prevention and treatment using a population-based macro simulation model: the MICADO model” 15 JUN 2015 DOI: 10.1111/dme.12811 Diabetic Medicine Volume 32, Issue 12, pages 1580–1587, December 2015

Michigan Model for Diabetes

Lead Presenter: Deanna Isaman

Other team members attending: William Herman, Stanley Kuo, and Michael Brandle

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 subject. 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 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 a user to control risk factor changes by defining treatment thresholds and compliance rates for hyperglycemia, dyslipidemia, and hypertension, and compliance to quitting smoking and taking aspirin.

Key Publications:

Ye W, Brandle M, Brown MB, Herman W. The Michigan Model for Coronary Heart Disease in Type 2 Diabetes: Development and Validation (2015). Journal of Diabetes Technology and Therapeutics 17(11) DOI: 10.1089/dia.2014.0304

Herman W, Ye W, Brown MB, Simmons R, Davies M, Khunti K, Rutten G, Sandbaek A, Lauritzen T, Borch Johnsen K, Wareham N (2015) 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. 38: 1449-1455

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

P Zhang, MB Brown, D Bilik, RT Ackermann, R Li, WH Herman (2012). 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* 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 Volume 13, Issue 2, April 2012, Pages 137-145

Barhak J, Isaman DJM, Ye W, Lee D: Chronic disease modelling and simulation software. Journal of Biomedical Informatics, Volume 43, Issue 5, October 2010, Pages 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 Volume 28, Number 16, Pages 2095 - 2115, 2009.

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; 28:2856-63.

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(8):2300-4.

Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, et al. Valuing health-related quality of life in diabetes. Diabetes Care. 2002;25(12):2238-43.

MMUs Diabetes Model

Lead Presenter: An Tran-Duy

Other team members attending: Philip Clarke

Brief Description:

The MMUs Diabetes Model is developed to simulate disease progression, predict occurrence of disease-related events and mortality, and estimate life expectancy and quality-adjusted life years in patients with type 2 diabetes. This is a probabilistic discrete-time model based on a set of parametric equations representing changes over time in risk factors and probabilities of events. The model can receive inputs in two forms: (1) vectors of fixed values of age, duration of diabetes, weight, height, total cholesterol, HDL cholesterol, systolic blood pressure and HbA1c, and vectors of fixed indicators of gender, ethnicity, smoking status and history of atrial fibrillation, peripheral vascular disease, ischemic heart disease, congestive heart failure, amputation, blindness, renal failure, ischemic stroke and acute myocardial infarction, or (2) parameters in the probability distributions of these variables.

Given the increasing chance that a patient survives after the first diabetes-related complication, and in anticipation of the availability of rich data coming from on-going and future observational studies (e.g. The Maastricht Study; see Eur J Epidemiol 2014;29:439- 51), this model is designed to allow prediction of repeated occurrence of the same diabetes- related complication and emergence of comorbidities (e.g. depression). The model is programmed in C++ with modern data structures and algorithms to maximize simulation speed and ease of incorporating new events, and minimize maintenance time. Integrated graphical user interfaces will be developed in the future to make the model a stand-alone program.

For the Mt Hood 2016 Challenge, the MMUs Diabetes Model uses the equations reported in the UKPDS Outcome Model (UKPDS 68).

Key Publications:

Not yet available

SPHR Diabetes

Lead Presenter: Penny Breeze

Other team members attending: Alan Brennan

Brief Description:

The SPHR Diabetes Prevention model is an individual patient simulation model programmed in R. It was developed 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 gain in diabetic or non-diabetic populations.

The model combines data from a number of sources to describe longitudinal risk factor trajectories and multiple complications and comorbidities relating to diabetes. BMI, HbA1c, systolic blood pressure, Total and HDL cholesterol trajectories have been estimated based on longitudinal data from the Whitehall II study. After progression to diabetes HbA1c trajectories are estimated using the UKPDS outcomes model.

A three stage diabetes treatment regimen is applied in the model. At diagnosis all patients are prescribed low cost treatments. If HbA1c increases above 7.4% the individual is prescribed the more expensive Gliptins in addition to Metformin. The individual continues to receive insulin above a threshold of 8.5%. Individuals receive opportunistic screening for hypertension and cardiovascular risk.

Cardiovascular events are estimated using the QRISK2 risk score to be representative of the UK population. In addition the risk of cardiovascular disease was assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS. Microvascular events are estimated from the UKPDS2 outcomes model. Other outcomes include Congestive Heart Failure, Breast cancer, Colorectal cancer, osteoarthritis and depression, cardiovascular mortality, cancer mortality and all-cause mortality. All health events incur costs and utility decrements.

Key Publications:

Breeze P, Squires H, Chilcott J, Stride C, Diggle PJ, Brunner E, Tabak A, Brennan A. (2015) A statistical model to describe longitudinal and correlated metabolic risk factors: the Whitehall II prospective study. Journal of Public Health. [Epub ahead of print].

Breeze PR, Thomas C, Squires H, Brennan A, Greaves C, Diggle PJ, Brunner E, Tabak A, Preston L, Chilcott J (2015) Impact of Type 2 diabetes prevention programmes based on risk identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. Diabetic Medicine. [Epub ahead of print]

The Reference Model

Lead Presenter: Jacob Barhak

Brief Description:

The Reference Model for Disease Progression is a validation model that employs High Performance Computing (HPC) to combine computational building blocks to best fit multiple populations. Those computational building blocks can be either other published models or assumptions. The Reference Model now employs an assumption engine that allows computational components to compete and cooperate to find better fitting model combination. The Reference Model is composed from multiple competing models, therefore its results show our mutual understanding of disease progression. The MIcro Simulation Tool (MIST) is used to support the model. MIST supports object oriented population generation which allow controlled modelling of populations from statistics and MIST runs over the cloud!

Key Publications:

J. Barhak, A. Garrett, W. A. Pruett, Optimizing Model Combinations, MODSIM world 2016. 26-28 Apr, Virginia Beach Convention Center, Virginia Beach, VA. Paper: http://www.modsimworld.org/papers/2016/Optimizing_Model_Combinations.pdf Presentation: http://sites.google.com/site/jacobbarhak/home/MODSIM2016_Submit_2016_04_25.pptx

J. Barhak, The Reference Model for Disease Progression and Latest Developments in the MIST, PyTexas 2015. College Station, TX, 26-Sep-2015. Presentation: http://sites.google.com/site/jacobbarhak/home/PyTexas2015_Upload_2015_09_26.pptx Video: https://www.youtube.com/watch?v=htGRRjia-QQ

J. Barhak, The Reference Model Uses Modular Population Generation! Object Oriented Population Generation on the Fly with MIST. IMAG Multiscale Modeling (MSM) Consortium Meeting 9-10 September 2015. Poster: http://sites.google.com/site/jacobbarhak/home/PosterModularPopulationGeneration_IMAG_MSM2015_Upload_2015_09_03.pdf

J. Barhak, The Reference Model uses Object Oriented Population Generation. SummerSim 2015 July 26-29, Chicago IL, USA. Paper: http://dl.acm.org/citation.cfm?id=2874946 Presentation: http://sites.google.com/site/jacobbarhak/home/SummerSim2015_Upload_2015_07_26.pptx

J. Barhak, Modeling Clinical Data from Publications, SpringSim 2015. April 12 - 15, Alexandria, VA, USA. Paper: http://dl.acm.org/citation.cfm?id=2873011&CFID=575392711&CFTOKEN=46270544 Presentation: http://sites.google.com/site/jacobbarhak/home/SpringSim2015ModelingDataFromPublications_Present_2015_04_13.pptx

J. Barhak, The Reference Model for Disease Progression – Data Quality Control. 6-10 July 2014, Monterey CA. Paper: http://dl.acm.org/citation.cfm?id=2685666 Presentation: http://sites.google.com/site/jacobbarhak/home/SummerSim2014_Upload_2014_07_06.pptx

J. Barhak, The Reference Model for Disease Progression uses MIST to find data fitness. PyData Silicon Valley 2014 held at Facebook Headquarters: Abstract: http://pydata.org/sv2014/abstracts/#195_ Presentation: http://sites.google.com/site/jacobbarhak/home/PyData_SV_2014_Upload_2014_05_02.pptx Video: https://www.youtube.com/watch?v=vyvxiljc5vA

J. Barhak, The Reference Model: Improvement in Treatment Through Time in Diabetic Populations, The Fourth International Conference in Computational Surgery and Dual Training. The Joseph B. Martin Conference Center at Harvard Medical School. Boston, MA, USA. December 9-10-11, 2012. Video: http://web.cs.uh.edu/~cosine/?q=node/140 , Presentation: http://www2.cs.uh.edu/~cosine/talks_cosine4/monday/MultidisciplinaryTalks/2_JacobBarhak.pptx Slides Copy: http://sites.google.com/site/ComputationalSurgery_Presneted_2012_12_LateUploadToOwnWebSite_2014_2_27.pptx

J. Barhak, The Reference Model for Disease Progression. SciPy 2012, Austin Tx, 18-19 July 2012. Paper: https://github.com/Jacob-Barhak/scipy_proceedings/blob/2012/papers/Jacob_Barhak/TheReferenceModelSciPy2012.rst, Poster: http://sites.google.com/site/jacobbarhak/home/PosterTheReferenceModel_SciPy2012_Submit_2012_07_14.pdf

UKPDS Outcomes Model

Lead Presenter: Jose Leal

Other team members attending: Philip Clarke and Alastair Gray

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, angina, stroke, heart failure, amputation, renal failure, diabetic ulcer and blindness in one eye) 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 diabetes simulation models.

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.

Appendix 1

Economics Modelling and Diabetes: Mount Hood 2016 Challenge

Challenge 1: Transparency Results

NOTE: The challenge results reported in this program represent work in progress and should not be reported or quoted without permission of the modelling groups.

	Gaps Identified					
	Cardiff	**ECHO-T2DM**	**IMS-CDM**	**MICADO**	**Michigan**	**The Reference Model**
Simulation Setting						
Sample Size - Assumption	Cohort of 1,000 patients	"The sample size(...) not presented" 1,000 cohorts x 2,000 patients		Cohort of 1,000 patients		Cohort of 1,000 patients
Time Horizon "Within trial" - Assumption		"The time horizon ("within trial") of the simulation was not specified. A median study follow-up of 10.4 years is mentioned elsewhere, but it is unclear what was run" Simulated 11 years as ECHO updates annual cycles				It is unclear from text if multiple simulations were conducted, separate for each end-point or one lifetime simulation. For simplicity, the 10 year period specified in UKPDS 33 under the findings section was used for those simulations. It is close enough to the 10.4 followup and 8.4 followup specified for the hypertentntion group in UKPDS 72.
Time Horizon "Projected - Assumption	80 years	Lifetime	Lifetime	60 years		It is unclear from text if multiple simulations were conducted, separate for each end-point or one lifetime simulation. The assumption is that one lifetime simulation was conducted per cohort.
Baseline Patient Characteristics						
Set of Patient Characteristics Used - Assumption	"The input parameters for the baseline population(...) not explicitly reported" Assumed from UKPDS 33	"We are uncertain what values and types of baseline patient characteristics were used." Assumed UKPDS 33	"Average patient profiles at UKPDS baseline and end of UKPDS follow-up (start of model projection are not reported)", "It is not stated if the modeling analysis employed in UKPDS 72 used individual patient level data or mean profiles" Assumed from UKPDS 33	No information in Clarke et al. UKPDS VIII	UKPDS 33	Lack of informartion in UKPDS 72 Assume UKPDS 33
Co-morbidities at baseline - Assumption	"The input parameters for the baseline population(...) not explicitly reported" Assumed none			No information in Clarke et al. Baseline population assumed uncomplicated since newly diagnosed type 2 diabetes patients. However will consult UKPDS VIII		Lack of informartion in UKPDS 72 Assume UKPDS 33
Treatment effect/thresholds	UKPDS 33					
HbA1c Intensification Treshold - Assumption		"We are not certain about what treatments were used during the "within trial" phase, including timing of switches" Ignored treatment switching intensification, Biomarkers simulated as described graphically in UKPDS 33 (HbA1c, SBP, BMI, with initial drift and annual drift) and UKPDS 80 (LDL, HDL, TC, annual drift calculated based on baseline value in UKPDS 80)				
Treatment Intensification - Assumption		"We are not certain about what treatments were used during the "within trial" phase, including timing of switches" Ignored treatment switching intensification, Biomarkers simulated as described graphically in UKPDS 33 (HbA1c, SBP, BMI, with initial drift and annual drift) and UKPDS 80 (LDL, HDL, TC, annual drift calculated based on baseline value in UKPDS 80)				
Initial HbA1c Treatment Effect and Drift over time - Assumption	"In order to obtain treatment effects for intensive versus conventional glucose control, Figure 2 from UKPDS 33 was digitised and conventional and intensive profiles for weight and HbA1c change were estimated" Based on UKPDS 33	"We are not certain about what treatments were used during the "within trial" phase, including timing of switches" Ignored treatment switching intensification, HbA1c simulated as described graphically in UKPDS 33	"Not reported in UKPDS 72" "No information is provided related to the shape/degree of risk factor change over time for HbA1c, blood pressure, BMI, and lipids" HbA1c progression for the first 10 years is assumed based on UKPDS 33, Figure 2. Beyond 10 years, we assumed progression based on UKPDS-68-HbA1c-panel-	"The scenario implied that actual HbA1c values at baseline were altered and then transition rates were set to 0 for a period of 10 year." MMD default trajectories	The trajectory of risk factors over time were partially available	Not reported in UKPDS 72 The change in A1c was extracted from UKPDS 33 Figure 3
Other Biomarker Treatment Effects and Drift over Time	"It was unclear how weight change over the projected period was handled"	"We are not certain about what treatments were used during the "within trial" phase,	"Not reported in UKPDS 72" "No information is provided related to the shape/degree of risk factor change over		The trajectory of risk factors over time were partially available	Not reported in UKPDS 72

Summary UKPDS 72

	Cardiff	ECHO-T2DM	IMS-CDM	MICADO	Michigan	The Reference Model
Cost						
Unit Cost	"It was also not clear how the implementation of unit costs and general practice related costs were being applied and how these related to the non-inpatient costs reported in UKPDS 65" "Cost of ESRD wasn't reported"	"We are uncertain as to which unit cost for macro- and microvascular were included in the analysis. The publication only presents cost for MI, stroke, and amputation. For remaining they refer to UKPDS 65"	"costs for fatal MI and fatal Stroke as complications costs. However, the outcomes model 1 (OM1) which was used for the model projection does not consider mortality specific to MI and/or stroke (…)", "Differences between unit costs for corresponding end points in UKPDS 72 vs. UKPDS 65 are likely due to inflation However, the equivalent time difference in years for which inflation was required is not reported (e.g. from 2000 to 2004?).", "No inflation rate was reported to convert cost estimates from UKPDS 65"	"Costs for blindness, ESRD were not provided"	"UKPDS 72 provided or cited event costs and ongoing costs for treatment of only some selected complications. For example, renal failure, diabetes mortality, and other-cause death were modelled in the UKPDS Outcomes Model, but neither UKPDS 72 nor UKPDS 65 provided costs for treatment or management of these complications", Inflate rate not reported	"Since UKPDS 72 did not have sufficient data, data was collected from multiple sources…"
- Assumption	Assumed from Baboola et al	Only included UKPDS 65 (macro- and microvascular)	We inflated costs based on the 18.6% difference of equivalent costs in UKPDS 72 and UKPDS 65.	We used as much as possible UK costs as provided, but this resulted in a lot of missing information. We added information from MH2012. (see table below	Assumed that these unreported costs were not included and thus assigned a cost of zero	UKPDS 65
Costs for Intervention and Comparator, "Wihin trial"	"The costs for therapy were specified per unit costs in UKPDS 72; however, the timing and distribution of pateints across therapies and dose applied was unclear" "It was not immediately clear that costs of therapy was only applied during the within-trial period"	"We are not certain about what treatments were used during the "within trial" phase, including timing of switches"	"No information on doses is provided which makes a reproduction of applied treatment costs based on dose impossible."	No information on units of resource use is provided in the paper	"Altough UKPDS 72 provided unit costs for antidabetic treatment, antihypertensive treatment, and standard care, it only cited the resource volume used aggregated over intervention groups"	"Since UKPDS 72 did not have sufficient data, data was collected from multiple sources…"
- Assumption	No therapy costs were modelled over the post-trial period	Unit treatment costs and resource usage were assumed to be weighted average of the cost for MET, SU, and insulin based on proportion assigned to MET, SU, and insulin in 23 centers in UKPDS 33 (Table 3)	Table 2, 3 and 4 provide however the total "within trial" cost of treatment which can be used to back calculate the annual treatment costs when average years alive in intensive and conventional treatment arm during UKPDS are sourced from UKPDS 68.		Assume standard of care in the US as modeled in the MMD	UKPDS 72
Costs for Intervention and Comparator, "Projected"			"It is unclear if the reported treatment costs from tables 2 to 4 represent "costs during the trial follow up period"…or if they represent lifetime treatment costs"			
- Assumption	No cost applied	No cost applied				
Anti-dylipidemia and anti-hypertensives		"The presentation of results suggests that anti-hypertensive treatment was applied, but the details were not presented in the methods section."			"it only cited the resource volume used aggregated over intervention groups"	"Since UKPDS 72 did not have sufficient data, data was collected from multiple sources…"
- Assumption	UKPDS 72	We assumed the proportional use of hypertensives to match the sub study in UKPDS 38 as UKPDS 33 doesn't present enough information on hypertensive treatments			"To estimate resource use, we could assume prescription dosages begin at the minimum standard of care in the US and are incremented per standard medical practice as modeled by the MMD."	UKPDS 72, 33, 38
Utility	"The disutility for end-stage renal disease was not specified"		"Utility data presented in UKPDS 72 are equivalent to the Tobit model for tariff (UKPDS 62) values but this is not clearly described in the UKPDS 72 paper."	Only a utility value for blindness in one eye is provided	Partly provided in UKPDS 72 and UKPDS 62; but information is not complete*	Partly provided in UKPDS 72
- Assumption	Assumed 0.307 from Lee et al	UKPDS 62		Utility weights for complications were taken from the paper	Assume discounting for ESRD is not used in UKPDS 72.	The utility score used was therefore chosen to be according to UKDPS 72 numbers

Summary Baxter

	Gaps Identified			
	Cardiff	**ECHO-T2DM**	**IMS-CDM**	**Michigan**
Simulation Setting				
# of Replications ("Sample Size") - Assumption		"The sample size(...) not presented" 1,000 cohorts x 2,000 patients		
Baseline Patient Characteristics				
Overall - Assumption	"The input parameters for the baseline population were not explicitly reported in baxter publications" T1DM Patients: Values from NICE NG 17 T2DM Patients: Values from NICE NG 28	"The manuscript does not report the baseline patient characteristics(...), it refers only to HbA1c subgroups" Sourced from NHANES stratified by HbA1c subgroups, supplemented from UKPDS when not in NHANES	"Baseline characteristics of the modeled populations are not reported" Assumed from NICE T2DM guidelines (NG 28)	"Baxter et al did not provide a detailed description the demographic characteristics of their population cohort, nor did they provide any reference to publications providing this information" Assumed from ADDITION or UKPDS
HbA1c Subgroups - Assumption	"No point estimates for HbA1c were provided within these ranges" 7.0%, 7.75%, 8.5% and 9.5%	"The manuscript does not report the baseline patient characteristics(...), it refers only to HbA1c subgroups" Assumed from NHANES: 6.35%, 7.68%, 8.43%, 10.56%	"Baseline characteristics of the modeled populations are not reported" Assumed from NICE T2DM guidelines (NG 28)	"(...) average baseline HbA1c distributions are unknown" Assumed from ADDITION or UKPDS
Treatment Effects/Thresholds				
HbA1c Intensification Threshold - Assumption	For T2DM: "Baxter et al. stated 'treatment levels specified by the NICE'" Assumed this to mean the NICE therapy escalation of threshold of 7.5% HbA1c	"Manuscript refers to HbA1c treatment intensification levels, but refers to other manuscripts (Kunthi et al. (2012, 2013, and 2014) and NICE guidelines for the values. We could not with any certainty figure out what values used based on reading other manuscript" Assumed 7.5% for the intensive arm (HbA1c target in NICE guideline for patients treated with MET+SU) and 9.0% for conventional arm (loosely based on clinical inertia in Khunti 2013). No explicit intensification of treatment occured	"It is unclear which particular therapy escalation thresholds were selected for the comparator arm" 7.5% for intensive arm (NICE guideline) and 8.7%, 9.1% and 9.7% for patients on 1, 2 or 3 OADs, respectively (from reference 9 in Baxter) for the conventional arm	
Treatment Intensification Sequence? - Assumption	No therapy changes were explicitly modelled	"It is unclear if there is a treatment algorithm with rescue treatment or not?" Not included	"No information provided on particular treatments types (e.g. Metformin, SU, insulin etc.)" "Treatment effects are described alongside assumed escalation thresholds but no HbA1c drops post therapy escalations are reported while it can be assumed that those were applied" An overall 1% point reduction in HbA1c for each therapy escalation	Michigan Model default treatment regimen
Initial HbA1c Treatment Effect - Assumption	For T2DM: "Treatment effects were not clearly outlined for the Type 2 analysis" T1DM: Initial HbA1c lowering for intensive arm (0.4% reduction), none for conventional T2DM: UKPDS 68 equation (if baseline HbA1c <7.5%), if HbA1c <7.5% initial HbA1c effect adjusted to land at 7.5%	"The treatment effects associated initially with the two treatment arms were not reported, but we are assuming there was one" Patients in "intensive" and "conventional" arm treated to achieve HbA1c of 7.0% and 9.0%, respectively	"It is stated that HbA1c was modeled alongside treatment modifications but the assumed effects of those treatment modifications are generally not reported" 1% point reduction (assumed from NICE guideline approach)	
	T1DM: "Baxter et al stated that the 'trajectory of HbA1c would follow the		"For type 1 it is stated that HbA1c was assumed to follow the natural history of HbA1c but for	

	Cardiff	ECHO-T2DM	IMS-CDM	Michigan
Prediction of complications				
Set of Macro- microvascular, and mortality equations - Assumption	"Specification of the source of equations/rates utilised in the prediction of long-term diabetes complications was not reported" T1DM: Cardiff defaults employed T2DM: UKPDS 82	"The risk equations used were not stated, and the CDM has the ability to run different risk equations" Used UKPDS 82 macrovascular and mortality risk equations	"No information provided" UKPDS 82 risk equations	
Hypoglycemia - Assumption	"Specification of the source of equations/rates utilised in the prediction of long-term diabetes complications was not reported" Rates from UK Hypoglycemic Study	Not considered		
Cost				
Macrovascular - Assumption	"Fatal costs for MI were not provided" Assumed fatal MI = non-fatal MI	Sourced from Baxter et al (2016)	Various sources	Provided in Baxter
Microvascular - Assumption	Cost of ESRD assumed from dialyusis or transplant based on Kerr et al Assumed costs for ulcers equivalent to those specified in Baxter for uncomplicated ulcer	Sourced from Baxter et al (2016)	Various sources	Provided in Baxter
Outcomes -Assumption		"We are unsure what units the cumulative incidence outcome (per person) is in Supplementary Table 3" Presented results of cumulative incidence on scale [0,1], in incremental differences		

The following are summaries of documentations submitted by the respective teams for Challenge 1

Study 1--Baxter et al.

Cardiff Model

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 utilizes 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.

We estimated the lifetime costs and cost savings associated with improving glycaemic control. For Type 1 diabetes this involved assessing the impact of a 0.4% reduction in HbA1c from a baseline of either 7.0%, 7.75%, 8.5% and 9.5%. For Type 2 diabetes, the same starting HbA1c values were used but the cost savings associated with managing patients held to a target of 7.5% were evaluated. Demographic and other risk factor profiles were matched to those reported in recent NICE guideline (NG17 and NG28). For both Type 1 and Type 2 models costs savings were calculated by estimating the reduction in complication rates compared to HbA1c held constant (Type 1 model) or HbA1c allowed to increase over time using the UKPDS 68 HbA1c panel equation.

Event costs (£2014) were applied in the year of occurrence and maintenance costs applied in all subsequent years. The costs of diabetes-related complications were drawn primarily from UKPDS 65 and utilities from UKPDS 62, and supplemented with Type 1-specific data where published.

Model output included the incidence of microvascular and macrovascular complications and their associated cumulative costs in 5-year increments to 25 years in total. Costs were undiscounted and were calculated at the per-patient level and extrapolated to the national level using UK population estimated for Type 1 and Type 2 diabetes.

ECHO-T2DM

The Economic and Health Outcomes Model of T2DM (ECHO-T2DM) was used to simulate the impact of "intensive" glucose control vs "conventional" glucose control for five subgroups of patients stratified by baseline HbA1c (HbA1c <7.5%; 7.5%≥ HbA1c ≤8.0; 8.0%≥HbA1c ≤ 9.0%, and HbA1c >9. ECHO-T2DM is a stochastic, multi-application, micro-simulation model developed for estimating the cost-effectiveness of treatment interventions, and it captures both first- and second-order uncertainty. Risks for macrovascular complications and mortality were modeled using UKPDS 82 risk equations [1]. Transition probabilities for microvascular health states are sourced from existing models and reflect differences in HbA1c levels and/or duration of T2DM [2-7]. Further details are provided elsewhere [8].

A total of 1,000 cohorts, each consisting of 2,000 hypothetical individuals with T2DM, were randomly generated and simulated over 25 years. Baseline patient characteristics were sourced from NHANES. Treatment consisted of two hypothetical agents with effect only on HbA1c. Patients in the "intensive" and "conventional" arms were treated in the first cycle to achieve a HbA1c of 7.5% and 9.0%, respectively (i.e., the HbA1c treatment effect were adjusted to meet these values), for each HbA1c stratification. No other treatment effects or biomarker drifts were simulated.

Unit costs for micro- and macrovascular complications were sourced from Baxter et al. 2016 [9] and reflect the UK healthcare perspective. They were not discounted. No other costs were considered. Utility decrements associated with disease complications were not included. Outcomes included total cost offset, cost offset per person, and difference in cumulative incidence of diabetes-related complications associated with "intensive" vs. "conventional" treatment.

Sensitivity analyses for 5, 10, 15, and 20 years' time horizon were conducted.

References

1. Hayes, A.J., et al., *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**(9): p. 1925-33.
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IMS-CDM

This study used the IMS-CORE-Diabetes-Model (CDM) (1) to estimate potential cost avoidance through modest and achievable improvements in glycaemic control in adults with Type 2 diabetes mellitus in the UK healthcare system. The impact of improved glycaemic control (indicated by reduction in HbA1c levels) was assessed by comparing treatment algorithms aiming to maintain HbA1c levels below NICE guideline recommendations (<7.5%) in comparison to therapy escalations commonly observed in UK clinical practice (UK-CP) at HbA1c thresholds ranging between 8.7%, 9.1% and 9.7% for patients on 1, 2 or 3 OADs, respectively (2). The cumulative incidence of microvascular and macrovascular complications was modelled across 5-year periods to a 25-year time horizon. The risk of cardiovascular complications and mortality was assessed utilizing risk equations from UKPDS-82. Complication costs were applied to projected per capita incidence rates and subsequently extrapolated to UK national level based on type-2-diabetes adult population estimates sourced from Cegedim-Strategic-Data (CSD Patient Data) UK-Ltd, MAT Aug 2014. Focus was attributed to cost savings associated with reduced complication rates while costs for interventions were not considered in this analysis. Costs for complications were derived from peer-reviewed literature and are summarized in table S1. No discounting was applied as the study was a budget impact analysis. Societal costs were not considered. Patient baseline characteristics were informed by UK type-2-diabetes profiles reported in a recent NICE guideline (NG28). Treatment modifications following NICE guideline recommendations vs. UK-CP were explored for four HbA1c baseline categories: 7.0%, 7.75% to 8.5%, and 9.5%. In each treatment scenario (NICE vs. UK-CP) we considered up to 7 possible escalations of hypothetical therapies, each of which resulting in a 1%-point HbA1c drop in the year of escalation. HbA1c progression in years post escalation was assumed based on UKPDS-68-HbA1c-panel-equation. Resulting HbA1c profiles alongside threshold specific therapy modifications are presented in Figure 1.

References

1- Andrew J. Palmer et al. The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Cost effectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making. CMRO VOL. 20, SUPPL 1, 2004, S5–S26

2- Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013; 36: 3411–3417.f

Study 2--UKPDS 72

Cardiff Model

The Cardiff Type 2 Diabetes Model is designed to estimate the long-term economic and health impact of managing patients with T2DM. The model is a fixed time increment (six-monthly) stochastic simulation with an 80-year time horizon; coded in C++ and linked to a Microsoft Excel front end. The model utilizes the UKPDS Outcomes Model equations (UKPDS 68 and 82) to predict macrovascular and microvascular complications and is designed to evaluate a treatment and control pathway, each of which are comprised of up to three lines of therapy. Therapeutic specific changes to HbA1c, cardiovascular risk factors, weight, rates of hypoglycaemia and adverse effects are translated into standard health economic output, most notably, time-dependent event rates, total costs, life years and quality adjusted life years (QALYs).

We estimated the lifetime costs and QALYs associated with conventional versus intensive blood glucose control observed in UKPDS. Treatment effects were applied to a cohort of 1,000 patients with simulated baseline characteristics matching those reported in the UKPDS 33. Table 1 reports the baseline characteristics and treatment effects applied. The evolution of modifiable risk factors (HbA1c, systolic blood pressure, total cholesterol to HDL ratio) followed trajectories reported in UKPDS 68. Annual treatment and implementation costs are presented in Table 2 along with costs of complications split into event cost applied in year of event and maintenance cost applied in each year after an event. Non-inpatient/outpatient costs are applied annually and are differentiated between those occurring pre or post any acute event. Health utility values used in the analysis are presented in Table 3.

Results are presented for a fully probabilistic lifetime analysis that considers the perspective of the UK NHS as payer. UK 2004 costs are presented, undiscounted and discounted (3.5% and 6.0%).

ECHO-T2DM

The Economic and Health Outcomes Model of T2DM (ECHO-T2DM) was used to simulate health and cost outcomes associated with “intensive” vs. “conventional” blood glucose control in the UKPDS over 75 years. ECHO-T2DM is a stochastic, multi-application, microsimulation model

developed for estimating the cost-effectiveness of treatment interventions and captures both first- and second-order uncertainty. Risks for macrovascular complications and mortality were estimated using UKPDS 68 risk equations [1]. Transition probabilities for microvascular health states are sourced from existing models and reflect differences in HbA1c levels and/or duration of T2DM [2-7]. Further details are provided elsewhere [8].

A total of 1,000 cohorts, each consisting of 2,000 hypothetical individuals with T2DM, were randomly generated and simulated over 75 years. Baseline patient characteristics were sourced from the UKPDS 33 study [9]. Treatment consisted of a "intensive" and "conventional" treatment arm, with treatment effects sourced from the UKPDS blood glucose study [9]. Treatment effects were applied for each patient in the intensive and conventional treatment arm in the first cycle, annual biomarker drifts were applied thereafter. From cycle 12 and onwards, biomarkers were held constant. No intensification or insulin rescue were applied. Proportion of populations treated with anti-hypertensives were sourced from UKPDS 38 [10].

UK-specific unit costs for micro- and macrovascular complications were sourced from UKPDS 65 and 72 [11], costs associated with intensive and conventional treatment, and costs for anti-hypertensive treatment were sourced from UKPDS 72; They reflect the UK payer perspective. Disutility weights were sourced from UKPDS 62 [12] and applied to baseline utilities for each year; they were additive when patients experienced multiple events in one cycle. Costs and quality-adjusted life-years (QALYs) were undiscounted.

Economic outcomes of this analysis included cost associated with treatment and complications, QALYs, incremental cost-effectiveness ratios, and cost-effectiveness acceptability curves.

Sensitivity analyses were conducted to evaluate different time horizon (11 years) and discount rates (3.5 % and 6.0 %).

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IMS-CDM

This study used the IMS CORE Diabetes Model (CDM) [1] to conduct a cost-utility analysis comparing intensive glucose control with insulin or sulfonylureas to conventional control (diet) as implemented in the UKPDS study (UKPDS 33). Patient baseline profiles at study enrollment were sourced from published sources (UKPDS 33) (Table1). Life time analyses (over 60 years) were conducted from the UK NHS perspective, including direct costs of diabetes related complications obtained from published sources and inflated to 2004 UK pounds sterling (£) (Table 2). Based on data reported in UKPDS 72, annual treatment and implementation costs were assumed at £388.5 and £177 for intensive and conventional glucose control, respectively. Health utility data applied in the modeling analysis were obtained from UKPDS 62 (Table 3). The risk of cardiovascular complications and mortality was assessed utilizing risk equations from UKPDS-68. The time progression HbA1c during the first 10 years of the analysis was based on progression patterns in patients with intensive and conventional control as reported in UKPDS 33. Beyond 10 years, HbA1c levels in both treatment strategies were assumed to converge to the same value and follow trajectories reported in UKPDS 68 (Figure 1). Incremental cost effectiveness ratios were assessed based on the net cost of healthcare resources associated with these policies and on effectiveness in terms of quality-adjusted life years gained. Costs and health outcomes were discounted at 0%, 3.5% and 6.0% per annum.

References

1- Andrew J. Palmer et al. The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Cost effectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making. CMRO VOL. 20, SUPPL 1, 2004, S5–S26

2- Beaudet A et al. Review of Utility Values for Economic Modeling in Type 2 Diabetes. Valule in Health 17 (2004) 462-470

MICADO

For the MICADO model evaluation, we concentrated on the intensive blood glucose control strategy. MICADO is a macro level state transition model. A more elaborate description of the MICADO model is available from van der Heijden et al. (2015). In short MICADO follows a diabetes cohort over time, covering the most important macrovascular and microvascular complications of diabetes as separate states, allowing for comorbidity by taking a marginal modeling approach [ref Hoogenveen et al.]. It was populated based on representative data from Dutch primary care registries and population studies for the base year 2003.

The intervention scenario was based on information found in the Clarke et al.(UKPDS 72) . In addition UKPDS VIII was consulted for missing information. For the reference scenario, we used the default settings of the MICADO model, but aimed to adjust HbA1c, and baseline complication rates to the values reported in Clarke et al. In the intervention scenario HbA1 was assumed to be regulated downward by intensive medical treatment with antidiabetics, during a period of 10 years. This was based on the reported UKPDS goal, an FPG of 6 mmol/l, using UKPDS VIII to find results in terms of HbA1c. Costs of intervention and complications were taken from Clarke et al. in UK£2004 and included medical costs only. Quality of life weights and decrements were based on Clarke et al. Complication rates were taken as estimated in the MICADO model. The model was run for a lifetime horizon (60 years), in a population with mean age 54 and 57% men. Baseline prevalence values and transition rates were set to the MICADO reference values for all risk factors except HbA1c at baseline, and at 11 years. HbA1c transitions were set to zero during the UKPDS follow-up period of 10 years in the intervention scenario. After this period, in both intervention scenario and reference scenario, an annual growth rate of 0.1% was assumed.

UKPDS Outcomes Model

The UKPDS Outcomes model (UKPDS-OM) version 1[1] and version 2[2] were used to replicate the cost-utility of intensive blood glucose control (sulphonylureas/insulin) compared to conventional blood glucose control (diet) reported in UKPDS 72. The perspective of the analysis was that of the NHS. The UKPDS Outcomes Model (UKPDS-OM) is a probabilistic directed time multi-state model simulating the occurrence in type 2 diabetic populations of eight diabetes-related complications and death to estimate quality-adjusted life expectancy, life expectancy, and costs.

We replicated the two groups of patients using UKPDS 33[3]. For risk factors not reported in UKPDS 33 (e.g. eGFR, white blood cell count), we assumed these to be the same as those reported in the LDS trial[4]. Patients were simulated over 40 years (UKPDS-OM version 1) and 70 years (UKPDS-OM version 2). Changes in HbA1c and weight during the 10 years of the trial were obtained from UKPDS 33 and used to model treatment effect. Beyond the trial period, we used the median HbA1c across the two interventions and applied it to both groups of patients. Changes in HbA1c beyond 10 years were modelled using the risk equations reported in UKPDS 68[1]. Changes in weight at 10 years were assumed to remain constant for the remainder of the simulation. We used the risk equations from UKPDS 68 to model the trajectory of systolic blood pressure, smoking status and LDL. The remaining risk factors were held constant from the start of the simulation. Intervention costs were derived from data reported in UKPDS 72. Complication costs were obtained from UKPDS 65[5] and inflated to 2004. Health utility scores were obtained from UKPDS 62[6]. When a patient experienced a complication, their utility was permanently decreased. We report undiscounted incremental costs, incremental QALYs and incremental cost-effectiveness ratio and compare both versions of the UKPDS-OM. Sensitivity analysis of the discount rates (3.5% and 6%) and trajectory of HbA1c and weight beyond 10 years was performed.

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Appendix 2

Economics Modelling and Diabetes: Mount Hood 2016 Challenge

Challenge 2: Communicating Outcomes Results

NOTE: The challenge results reported in this program represent work in progress and should not be reported or quoted without permission of the modelling groups.

Table: Life Expectancy

MEN — **Non-Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
UKPDS (Leal et al., 2009)			14.50	14.00	13.70	13.10	12.90	14.00	13.30	12.80	12.50	12.00	13.00	12.40	11.80	11.60	11.10
Cardiff Model (UKPDS82)	SBP	140	17.21	17.01	16.74	16.28	15.55	16.78	16.55	16.25	15.74	14.94	16.04	15.79	15.45	14.88	14.00
ECHO-T2DM	SBP	140	14.17	13.62	13.05	12.52	11.91	13.52	12.84	12.17	11.52	10.90	12.61	11.88	11.12	10.47	9.77
MICADO	SBP	140	10.17	10.07	9.94	9.80	9.80	9.89	9.76	9.61	9.44	9.44	9.75	9.60	9.42	9.23	9.23
Michigan Model for Diabetes	SBP	140	17.34	16.66	16.01	15.37	14.65	16.71	15.61	14.69	14.13	13.53	15.59	14.46	13.32	12.87	11.92
MMUs Diabetes Model	SBP	140	13.23	11.39	10.08	8.82	7.73	11.89	9.90	8.48	7.19	6.30	10.13	8.27	7.00	5.99	5.33
SPHR Diabetes	SBP	140	15.54	15.31	15.15	14.95	14.78	15.23	15.07	14.82	14.67	14.44	15.03	14.75	14.54	14.37	13.66
The Reference Model*	SBP	140	16.55	16.03	15.62	14.89	14.47	16.12	15.64	15.25	14.70	14.04	15.83	15.45	15.02	14.30	13.89
			4.00	5.00	6.00	7.00	8.00	4.00	5.00	6.00	7.00	8.00	4.00	5.00	6.00	7.00	8.00
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	15.42	14.86	14.30	13.74	13.18	14.63	13.95	13.30	12.66	12.04	13.61	12.84	12.10	11.40	10.76
IMS CORE Diabetes Model	SBP	140	14.91	14.60	14.18	13.48	12.41	14.20	13.86	13.34	12.67	11.57	13.16	12.82	12.34	11.61	10.53
MDM–TTM	SBP	140	15.72	15.54	15.30	14.90	14.25	15.21	15.01	14.76	14.30	13.59	14.63	14.41	14.11	13.62	12.85
UKPDS Outcomes Model	SBP	140	16.86	16.66	16.40	15.88	15.04	16.51	16.22	15.94	15.36	14.47	15.87	15.68	15.26	14.75	13.82
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

WOMEN — **Non-Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
UKPDS (Leal et al., 2009)			16.00	15.80	15.40	15.30	15.00	15.60	15.20	15.00	14.60	14.20	14.90	14.50	14.30	13.80	13.40
Cardiff Model (UKPDS82)	SBP	140	18.97	18.85	18.47	17.85	16.75	18.66	18.53	18.13	17.46	16.28	18.28	18.14	17.71	16.99	15.73
ECHO-T2DM	SBP	140	15.97	15.65	15.21	14.82	14.43	15.47	15.01	14.50	14.07	13.58	14.72	14.17	13.63	13.11	12.55
MICADO	SBP	140	11.36	11.26	11.15	11.01	11.01	11.10	10.99	10.84	10.68	10.68	10.99	10.86	10.70	10.52	10.52
Michigan Model for Diabetes	SBP	140	19.22	18.66	18.47	18.10	17.58	18.64	18.19	17.93	17.39	16.78	18.38	17.60	16.94	16.51	15.73
MMUs Diabetes Model	SBP	140	16.86	15.97	14.98	14.11	12.97	16.15	14.85	13.74	12.42	11.19	14.95	13.74	12.13	10.67	9.58
SPHR Diabetes	SBP	140	17.68	17.42	17.22	17.07	16.81	17.40	17.22	16.98	16.68	16.53	17.17	16.90	16.73	16.43	16.11
The Reference Model*	SBP	140	18.49	18.04	17.62	17.12	16.76	18.38	17.79	17.30	16.94	16.37	17.95	17.65	17.13	16.64	16.18
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	16.46	16.15	15.82	15.48	15.13	15.93	15.53	15.12	14.70	14.28	15.18	14.69	14.19	13.70	13.20
IMS CORE Diabetes Model	SBP	140	16.56	16.40	15.90	15.18	13.91	15.94	15.73	15.26	14.43	13.20	14.92	14.74	14.27	13.49	12.20
MDM–TTM	SBP	140	17.74	17.65	17.31	16.71	15.62	17.37	17.27	16.88	16.24	15.08	16.91	16.80	16.38	15.70	14.46
UKPDS Outcomes Model	SBP	140	18.67	18.51	18.15	17.45	16.18	18.33	18.22	17.80	17.03	15.76	17.98	17.81	17.35	16.55	15.20
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

*No temporal correction

Table: Life Expectancy

MEN

Smoker

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
UKPDS (Leal et al., 2009)			12.60	12.20	11.70	11.40	10.90	11.90	11.60	11.10	10.80	10.50	11.20	10.60	10.20	9.90	9.40
Cardiff Model (UKPDS82)	SBP	140	13.95	13.75	13.48	13.03	12.31	13.51	13.29	13.00	12.50	11.71	12.94	12.67	12.32	11.75	10.88
ECHO-T2DM	SBP	140	12.51	11.91	11.33	10.78	10.25	11.78	11.13	10.47	9.88	9.26	10.97	10.25	9.53	8.86	8.21
MICADO	SBP	140	9.42	9.29	9.12	8.94	8.94	9.07	8.90	8.70	8.49	8.49	8.84	8.65	8.44	8.20	8.20
Michigan Model for Diabetes	SBP	140	16.49	15.57	14.69	14.28	13.39	15.47	14.38	13.23	12.80	11.91	14.22	12.95	11.81	11.43	10.50
MMUs Diabetes Model	SBP	140	12.03	10.31	8.71	7.46	6.55	10.68	8.84	7.28	6.20	5.28	9.21	7.31	5.98	5.06	4.31
SPHR Diabetes	SBP	140	15.12	14.93	14.71	14.52	14.27	14.88	14.65	14.42	14.21	13.95	14.57	14.32	14.10	13.88	13.64
The Reference Model*	SBP	140	14.28	13.93	13.38	13.00	12.30	14.20	13.64	13.10	12.65	12.02	13.83	13.30	12.75	12.34	11.79
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	13.62	13.06	12.50	11.96	11.44	12.84	12.17	11.54	10.94	10.37	11.87	11.51	10.43	9.79	9.21
IMS CORE Diabetes Model	SBP	140	13.95	13.63	13.14	12.47	11.38	13.22	12.88	12.36	11.63	10.51	12.18	11.83	11.31	10.61	9.50
MDM–TTM	SBP	140	13.37	13.21	12.99	12.62	12.03	12.91	12.72	12.48	12.07	11.43	12.37	12.17	11.90	11.46	10.76
UKPDS Outcomes Model	SBP	140	13.94	13.77	13.48	13.01	12.31	13.56	13.28	13.01	12.55	11.77	13.08	12.81	12.51	11.95	11.16
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

WOMEN

Smoker

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
UKPDS (Leal et al., 2009)			14.30	14.20	13.70	13.40	13.10	13.90	13.60	13.00	12.90	12.50	13.30	12.60	12.30	11.90	11.70
Cardiff Model (UKPDS82)	SBP	140						15.52	15.40	14.99	14.31	13.15	15.09	14.96	14.50	13.77	12.51
ECHO-T2DM	SBP	140	14.27	13.96	13.55	13.08	12.72	13.80	13.36	12.81	12.33	11.85	13.10	12.56	11.99	11.44	10.92
MICADO	SBP	140	10.58	10.45	10.28	10.07	10.07	10.21	10.05	9.84	9.59	9.59	10.01	9.83	9.60	9.32	9.32
Michigan Model for Diabetes	SBP	140	18.61	18.12	17.81	17.33	16.55	17.97	17.40	17.11	16.40	15.80	17.25	16.50	15.82	15.12	14.38
MMUs Diabetes Model	SBP	140	14.96	13.82	12.78	11.64	10.70	14.13	12.68	11.39	10.21	9.26	12.91	11.30	9.79	8.63	7.73
SPHR Diabetes	SBP	140						16.81	16.52	16.31	16.04	15.82	16.48	16.24	15.99	15.67	15.46
The Reference Model*	SBP	140	16.20	15.89	15.28	14.68	14.46	16.00	15.42	15.09	14.68	14.15	15.74	15.26	14.74	14.33	13.71
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140						14.19	13.78	13.37	12.95	12.53	13.48	12.98	12.48	12.00	11.51
IMS CORE Diabetes Model	SBP	140	15.81	15.62	15.16	14.36	13.07	15.17	14.98	14.46	13.63	12.31	14.16	13.97	13.45	12.64	11.36
MDM–TTM	SBP	140	15.19	15.10	14.76	14.21	13.19	14.82	14.72	14.37	13.76	12.68	14.40	14.30	13.91	13.25	12.10
UKPDS Outcomes Model	SBP	140	15.63	15.50	15.09	14.45	13.32	15.30	15.17	14.75	14.07	12.82	14.83	14.79	14.34	13.60	12.36
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

*No temporal correction

Table: Lifetime QALY

MEN — **Non-Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
Cardiff Model (UKPDS82)	SBP	140	14.43	14.24	13.98	13.55	12.86	13.98	13.76	13.48	13.00	12.26	13.18	12.95	12.64	12.13	11.33
ECHO-T2DM			11.16	10.73	10.28	9.88	9.40	10.58	10.04	9.52	9.04	8.55	9.75	9.21	8.63	8.15	7.62
MICADO			9.29	9.13	8.94	8.73	8.73	8.93	8.73	8.50	8.24	8.24	8.73	8.51	8.25	7.96	7.96
Michigan Model for Diabetes			12.60	11.77	11.05	10.59	9.96	11.66	10.53	9.72	9.33	8.80	10.60	9.59	8.74	8.41	7.73
MMUs Diabetes Model			5.89	5.79	5.70	5.34	4.92	5.88	5.57	5.21	4.68	4.21	5.59	5.12	4.61	4.04	3.66
SPHR Diabetes			9.44	9.25	9.11	8.94	8.77	9.08	8.93	8.74	8.59	8.38	8.85	8.63	8.45	8.29	7.67
The Reference Model*			12.35	11.91	11.55	10.99	10.66	12.04	11.62	11.30	10.85	10.34	11.81	11.48	11.12	10.55	10.23
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	13.00	12.50	11.99	11.49	11.00	12.25	11.65	11.07	10.51	9.97	11.29	10.61	9.98	9.38	8.83
IMS CORE Diabetes Model			11.08	10.83	10.51	9.96	9.14	10.35	10.09	9.69	9.20	8.37	9.42	9.17	8.82	8.29	7.51
MDM–TTM			12.04	11.90	11.72	11.40	10.90	11.60	11.45	11.25	10.90	10.35	11.10	10.93	10.71	10.33	9.74
UKPDS Outcomes Model			13.33	13.17	12.95	12.53	11.85	13.00	12.76	12.53	12.07	11.34	12.41	12.26	11.92	11.51	10.77
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

WOMEN — **Non-Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
Cardiff Model (UKPDS82)	SBP	140	16.24	16.11	15.76	15.18	14.16	15.91	15.78	15.40	14.78	13.70	15.50	15.37	14.96	14.30	13.15
ECHO-T2DM			10.87	10.67	10.36	10.12	9.82	10.44	10.14	9.80	9.52	9.20	9.80	9.45	9.12	8.76	8.40
MICADO			10.44	10.30	10.12	9.91	9.91	10.11	9.94	9.73	9.47	9.47	9.96	9.77	9.54	9.25	9.25
Michigan Model for Diabetes			13.97	13.40	13.07	12.54	12.05	12.99	12.47	12.03	11.50	10.88	12.52	11.72	11.20	10.70	10.02
MMUs Diabetes Model			6.08	6.31	6.50	6.68	6.60	6.33	6.50	6.72	6.55	6.26	6.46	6.71	6.52	6.14	5.76
SPHR Diabetes			10.48	10.30	10.13	9.98	9.78	10.20	10.05	9.84	9.63	9.49	9.97	9.76	9.61	9.37	9.14
The Reference Model*			13.90	13.49	13.14	12.73	12.43	13.82	13.32	12.89	12.60	12.16	13.48	13.21	12.77	12.39	12.03
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	14.07	13.78	13.47	13.16	12.84	13.52	13.16	12.78	12.41	12.02	12.75	12.31	11.88	11.44	11.01
IMS CORE Diabetes Model			12.38	12.25	11.86	11.30	10.33	11.67	11.51	11.15	10.53	9.62	10.73	10.59	10.25	9.68	8.74
MDM–TTM			13.67	13.59	13.32	12.85	12.01	13.34	13.26	12.96	12.45	11.56	12.94	12.85	12.53	12.00	11.04
UKPDS Outcomes Model			14.86	14.72	14.42	13.85	12.82	14.55	14.46	14.10	13.48	12.46	14.22	14.08	13.70	13.05	11.96
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

*No temporal correction

Table: Lifetime QALY

MEN — **Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
Cardiff Model (UKPDS82)	SBP	140	11.68	11.50	11.25	10.83	10.18	11.24	11.04	10.77	10.32	9.60	10.66	10.42	10.09	9.58	8.80
ECHO-T2DM			9.90	9.42	8.97	8.55	8.12	9.26	8.75	8.26	7.79	7.32	8.54	8.00	7.45	6.94	6.44
MICADO			8.42	8.21	7.96	7.69	7.69	7.95	7.70	7.41	7.09	7.09	7.65	7.37	7.05	6.69	6.69
Michigan Model for Diabetes			11.64	10.75	10.01	9.68	8.97	10.45	9.55	8.68	8.34	7.72	9.48	8.50	7.69	7.43	6.80
MMUs Diabetes Model			5.32	5.22	4.97	4.60	4.24	5.29	5.02	4.53	4.07	3.58	5.09	4.53	3.98	3.47	2.99
SPHR Diabetes			9.08	8.92	8.73	8.55	8.34	8.77	8.57	8.38	8.19	7.97	8.47	8.24	8.05	7.86	7.65
The Reference Model*			10.66	10.33	9.89	9.57	9.04	10.60	10.14	9.69	9.33	8.86	10.33	9.88	9.45	9.11	8.67
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140	11.46	10.95	10.46	9.98	9.51	10.73	10.14	9.59	9.06	8.57	9.83	9.51	8.59	8.04	7.54
IMS CORE Diabetes Model			10.36	10.11	9.73	9.21	8.37	9.62	9.37	8.98	8.44	7.61	8.71	8.46	8.08	7.57	6.76
MDM–TTM			10.25	10.12	9.95	9.66	9.20	9.85	9.71	9.52	9.20	8.70	9.40	9.25	9.03	8.69	8.16
UKPDS Outcomes Model			11.04	10.90	10.65	10.27	9.70	10.69	10.46	10.25	9.87	9.23	10.25	10.03	9.79	9.35	8.71
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

WOMEN — **Smoker**

			HbA1c (6%)					HbA1c (8%)					HbA1c (10%)				
Cardiff Model (UKPDS82)	SBP	140						13.24	13.12	12.75	12.13	11.07	12.80	12.68	12.26	11.59	10.46
ECHO-T2DM			9.78	9.55	9.28	8.95	8.73	9.36	9.09	8.73	8.39	8.05	8.77	8.43	8.05	7.70	7.37
MICADO			9.51	9.30	9.05	8.73	8.73	9.03	8.78	8.48	8.11	8.11	8.77	8.50	8.17	7.76	7.76
Michigan Model for Diabetes			13.29	12.71	12.32	11.78	11.08	12.31	11.58	11.28	10.59	10.03	11.57	10.77	10.20	9.57	8.98
MMUs Diabetes Model			5.50	5.62	5.74	5.78	5.68	5.65	5.70	5.74	5.58	5.45	5.69	5.74	5.46	5.23	4.91
SPHR Diabetes								9.72	9.50	9.30	9.08	8.89	9.42	9.22	9.01	8.76	8.57
The Reference Model*			12.17	11.89	11.40	10.92	10.72	12.01	11.53	11.24	10.89	10.48	11.82	11.41	10.98	10.64	10.16
			4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
			Cholesterol (Total:HDL)														
Cardiff Model (UKPDS68)	SBP	140						12.03	11.66	11.28	10.90	10.52	11.31	10.87	10.43	10.00	9.58
IMS CORE Diabetes Model			11.82	11.67	11.30	10.69	9.69	11.10	10.96	10.57	9.95	8.97	10.18	10.04	9.66	9.07	8.14
MDM–TTM			11.70	11.63	11.36	10.93	10.14	11.38	11.31	11.04	10.56	9.71	11.03	10.95	10.64	10.13	9.24
UKPDS Outcomes Model			12.46	12.34	12.00	11.48	10.57	12.16	12.05	11.71	11.15	10.14	11.74	11.70	11.33	10.74	9.73
			0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20	0.40	0.35	0.30	0.25	0.20
			Cholesterol (HDL:LDL)														

*No temporal correction

The following are summaries of documentations submitted by the respective teams for Challenge 2

Cardiff Model

Abbreviations

BMI	body mass index
CHF	congestive heart failure
CVD	cardiovascular disease
ESRD	end-stage renal disease
HbA1c	haemoglobin A1c
HDL	high density lipoprotein
IHD	ischaemic heart disease
LDL	low density lipoprotein
MI	myocardial infarction
QALY	quality adjusted life years
SBP	systolic blood pressure

Section 1 Inputs and assumptions

Model set-up

- Inputs provided in the Excel file were incorporated into the Cardiff Type 2 Diabetes Model and used as default settings
- Analysis was run using UKPDS 68[1] and UKPDS 82[2] risk equations, and both sets of results are provided
- Discounting was set to 0%, as instructed
- The model was run over a 40-year time horizon, which was considered to be lifetime
- Risk factors were kept constant, as instructed
- Treatment effects were set to null values
- Analysis was run for all 55 subjects identified in the input sheet

Assumptions

Limited assumptions were required to implement this challenge; these are documented in Table 1.

Table 1: Table of assumptions

No.	Assumption
1	Modelled results over a 40-year time horizon
2.	CVD was calculated by summing the rates of IHD, MI, stroke and CHF

3.	No prior clinical history was assumed
4.	We used an age adjusted baseline utility based on an equation derived from the Health Survey for England 2003
5.	We did not model any treatment escalation
6.	Ethnicity =1 is Caucasian We have assumed that when ethnicity is set to 1 it refers to a 100% Caucasian population.

CHF: congestive heart failure; CVD: cardiovascular disease; IHD: ischaemic heart disease; MI: myocardial infarction

Section 2 Data gaps

- The choice of baseline utility was not explicitly stated, therefore the Cardiff Model's defaults baseline utility was used: an age-adjusted baseline utility based on the HSE equation, see below.
- The number of runs was not stipulated in the provided information and so we chose to run the analysis for 5,000 runs, for a cohort size of 5,000 to ensure that our results would stabilize.

Age-dependent baseline utility

The relationship between age and baseline utility was modelled using mean EQ-5D by age group in subjects with no major complications, obtained from the Health Survey for England 2003.

The polynomial in Figure 1 shows the inverse relationship estimated between age and utility, in which utility decreases as age increases. At the beginning of the simulation, all patients are assigned a baseline utility value dependent on baseline age in accordance with this relationship.

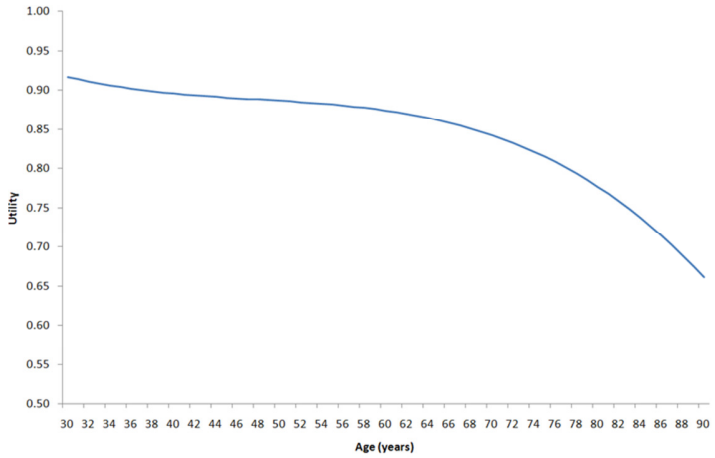

Figure 1: Age-dependent baseline utility function

References

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3. Department of Health. Health Survey for England 2003. Available at: http://www.dh.gov.uk/PublicationsAndStatistics/PublishedSurvey/HealthSurveyForEngland/HealthSurveyResults/HealthSurveyResultsArticle/fs/en?CONTENT_ID=4098913&chk=4DPdlh, [Accessed November 2013].

IMS-CORE Diabetes Model

Approach

- We used version 9.0 of the IMS CORE Diabetes model
- Discounting set to 0%
- Life-time horizon (60 years).
- Set up a simulation matching all inputs in the specified Excel sheet.
- All risk factors (HbA1c, blood pressure, lipids etc.) were hold constant over time.
- We applied the model using UKPDS 82 risk equations for cardiovascular end point and mortality predictions.
- We applied utilities as reported in Beaudet et al. 2014 (1)
- The CORE minimum approach was selected to estimate quality adjusted life expectancy (the minimum approach employs the value of the condition with the lowest individual utility score)
- Each risk factor scenario was projected for 1000 patients in 250 bootstrap iterations
- Applied cohort characteristics are presented in table 1

Table 1: Cohort characteristics applied in the modelling

Variable	Mean	Units	Reference
PATIENT DEMOGRAPHICS			
Start age	65	years	Excel specification
Duration of Diabetes	5	years	Excel specification
Prop. Male	Variable	[0-1]	Excel specification
BASELINE RISK FACTORS			
HbA1c	Variable	%-points	Excel specification
SBP	140	mmHg	Excel specification
DBP	82		UKPDS 33 Table 1
T-CHOL	Variable	mg/dL	Excel specification

HDL	1	mmol/L	Excel specification
LDL	Variable	mg/dL	Excel specification
TRIG	162	mg/dL	UKPDS 33 Table 1 (column 3, All patients)
BMI	29.8	kg/m2	Excel specification
eGFR	74	ml/min/1.73m2	Excel specification
Haemoglogin	13,9	gr/dl	CDM default (from UKPDS 82)
White blood cell count	6,9	106/ml	Excel specification
Heart rate	82.2	bpm	Excel specification
Waist to hip ratio	0,93	(1 unit)	CDM default
Urinary albumin excretion rate	3,1	mg/mmol	CDM default
Serum Creatinine	1,1	mg/dl	CDM default
Serum albumin	3,9	g/dl	CDM default
Prop. smoker	Variable	[0-1]	Excel specification
Cigarettes/day	10		Assumption
Alcohol consumption	0	Oz/week	Assumption
Baseline complication history	0%	%	History of micro and macrovascular complications was set to zero.

References

1) Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes.Value Health. 2014 Jun; 17(4):462-70.

ECHO-T2DM

As per instruction

- We replicated the life tables of UKPDS patients in Leal et al. (2009) using ECHO-T2DM
  - As per instructions we ran 55 simulations, each simulation with a specific set of biomarker covariates altering gender, smoking status, SBP, lipids, HbA1c, BMI, eGFR, WBC and heart rate available in the attached "Challenge 2 Input Sheet".
- As per instructions, outputs on the following were generated: QALYs, and cumulative incidence for MI, Stroke, CHF, Overall CVD, ESRD, and Amputation.
- Baseline patient characteristics were mainly sourced from the attached "Challenge 2 Input Sheet"
  - For specific details, see
  - Table *1* (note that only the characteristics for ID 1 of 60 is presented)
- No treatment included, as per instructions
  - However, the provided inputs table, entitled "Challenge 2 Input Sheet", indicate that BMI was decreased by 1.4 and 0.5 kg/m^2 in cycle 10 for females and males respectively. As such, our simulations reflected that as well.
- Simulations were lifetime projections (as per instructions), we used a 36-year time horizon as to make sure that all patients die at the age of 100
- A total of 1,000 cohorts of 2,000 unique hypothetical patients were simulated in each of the simulations
- As per instructions, QALYs were not discounted
- We used the UKPDS 68 macrovascular and mortality risk equations, as Leal et al (2009) use UKPDS-OM1

The following were unclear:

- Baseline Patient Characteristics
  - Proportion patients with baseline co-morbidities not included in the instructions were assumed from UKPDS 33, and if not available there we assumed 0
- QALY disutility weights
  - The instruction included results for QALY but as no QALY weights were included in the instruction or the Leal et al. (2009) publication we assumed the TTO model from the CODE-2 study [1], see Table 2

To fit the ECHO-T2DM, we had to do the following:

- Baseline Patient Characteristics
  - Cholesterol was presented as mmol/l in the instruction data file. To fit the ECHO-T2DM structure we converted the cholesterol to mg/dl.
  - ECHO-T2DM structure included baseline triglycerides which was not included in the instruction data file. Mean baseline triglycerides were calculated based on the Friedewald equation
- Biomarker evolution

- No events of ESRD occurred in our simulations as the definition of ESRD in ECHO-T2DM is defined as having an eGFR<15 and in line with the instructions, eGFR was held constant over the course of the simulation.

Table 1: Baseline Patients Characteristics

Parameter	Mean/%	Comments
Varying Inputs		
Age	**65.00**	**As in the instructions (ID 1)**
Gender	**Female**	**As in the instructions (ID 1)**
Smoking (Yes/no)	**No**	**As in the instructions (ID 1)**
HbA1c (%)	**6.00**	**As in the instructions (ID 1)**
Total Cholesterol (mg/dL)	**185.33**	**As in the instructions (ID 1)**
LDL Cholesterol (mg/dl)	**115.83**	**As in the instructions (ID 1)**
HDL Cholesterol (mg/dl)	**38.61**	**As in the instructions (ID 1)**
Triglycerides (mg/dl)	**115.83**	**Use Friedwald equation**
SBP (mmHg)	**140.00**	**As in the instructions (ID 1)**
BMI (kg/m2)	**29.80**	**As in the instructions (ID 1)**
eGFR (ml/min/1.73m2)	**67.89**	**As in the instructions (ID 1)**
WBC (*10^6)	**6.80**	**As in the instructions (ID 1)**
HR (beat/minute)	**82.20**	**As in the instructions (ID 1)**
Non-varying Inputs		
Demographics		
Disease duration (years)	**5.00**	**As in the instructions**
<u>Ethnicity/Race (%)</u>		
African Americans	**0.00**	**As in the instructions**
American Indians	**0.00**	**As in the instructions**
Hispanics	**0.00**	**As in the instructions**

Parameter	Mean/%	Comments
Indians	0.00	As in the instructions
Clinical indicators		
Proportion Patients with Atrial Fibrillation (AF)	0.00	As in the instructions
Co-morbidities (Proportion)		
<u>Retinopathy</u>		
Proportion Patients with BDR	0.36	Instructions say source from UKPDS 33 (Turner et al (1998), table 1, p. 839: assumption "Retinopathy")
Proportion Patients with ME	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with ME and Blindness in One Eye	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with PDR	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with PDR and Blindness in One Eye	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with ME and PDR	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with ME, PDR and Blindness in One Eye	0.00	Instructions say source from UKPDS 33 (UKPDS 33 Inclusion Criteria)
Proportion Patients with Blindness in One Eyes	0.00	As in the instructions
Proportion Patients with Blindness in Both Eyes	0.00	As in the instructions
<u>CKD</u>		
Proportion Patients with Microalbuminuria	0.00	As in the instructions
Proportion Patients with Macroalbuminuria	0.00	As in the instructions
Proportion Patients with ESRD	0.00	"Renal" in instructions

Parameter	Mean/%	Comments
Neuropathy		
Proportion Patients with Symptomatic Neuropathy	0.00	Instructions say source from UKPDS 33. Not there, assume 0?
Proportion Patients with PVD	0.00	As in the instructions
Proportion Patients with Symptomatic Neuropathy and PVD	0.00	Instructions say source from UKPDS 33. Not there, assume 0?
Proportion Patients with Diabetic Foot Ulcer	0.00	Instructions say source from UKPDS 33. Not there, assume 0?
Proportion Patients with History of 1 Previous LEA	0.00	As in the instructions
Proportion Patients with History of >=2 Previous LEA's	0.00	As in the instructions
Macrovascular		
Proportion with IHD	0.00	As in the instructions
Proportion with MI	0.00	As in the instructions
Proportion with CHF	0.00	As in the instructions
Proportion with Stroke	0.00	As in the instructions

Table 2: Utility Decrements Associated with Long Term Modeled Diabetic Complication Health States

Complication	Utility Decrement		Source
Patient Characteristics	Mean	SE	
Age (per 10 Years)	-0.0235	0.001	CODE 2
Female	-0.0930	0.009	CODE 2
Duration of DM (per 10 Years)	-0.0163	0.001	CODE 2
Macrovascular Complications			
IHD	-0.0280	0.010	CODE 2
MI	-0.0280	0.010	CODE 2

HF	**-0.0280**	**0.010**	**CODE 2**
Stroke	**-0.1150**	**0.017**	**CODE 2**
Microvascular Complications			
Retinopathy (incl. combinations)	**0.0000**	**1E-99**	**CODE 2**
Blindness (one or both eyes, incl. combinations)	**-0.0570**	**0.022**	**CODE 2**
Microalbuminuria	**0.0000**	**1E-99**	**Excl from CODE 2**
Gross Proteinuria	**-0.0480**	**0.022**	**CODE 2**
Symptomatic Neuropathy	**-0.0840**	**0.014**	**CODE 2**
Peripheral Vascular Disease (PVD)	**-0.0610**	**0.015**	**CODE 2**
Symptomatic Neuropathy & PVD	**-0.0850**	**0.018**	**CODE 2**
Diabetic Foot Ulcer	**-0.1700**	**0.019**	**CODE 2**
One Lower Extremity Amputation	**-0.2720**	**0.029**	**CODE 2**
Two Lower Extremity Amputations	**-0.2720**	**0.029**	**CODE 2**
Obesity			
Per 1 BMI > 25kg/m^2	**-0.0061**	**0.001**	**CODE 2**

Reference

1. Bagust, A. and S. Beale, *Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data.* Health Econ, 2005. 14(3): p. 217-30.

MICADO

Demographic characteristics:

- The following demographic characteristics were included in MICADO:
  - Gender
  - Age
  - BMI
- The following demographic characteristics were **not** included in MICADO:
  - Ethnicity, duration of diabetes, weight, and height.
  - Duration of diabetes was not of influence on the outcomes in MICADO. IN MICADO duration affects initial prevalence numbers for complication stages.

However, these were set to zero as part of the characteristics of the example patients. Only uncomplicated patients at baseline were evaluated.

Current risk factor values:

- The following current risk factors were included in MICADO:
  - Smoking
  - Cholesterol level (total cholesterol)
  - Systolic Blood Pressure
  - HbA1c
- The following current risk factors were **not** included in MICADO:
  - Atrial fib., PVD, micro/macroabluminuria, total:HDL ratio, HDL:LDL ratio, HDL, LDL, WBC, eGFR, Heart rate and haemoglobin.

Years since pre-existing event

- *Initial prevalence numbers for complications* were set to zero for all micro- and macrovascular complications. That is, our population is complication-free at baseline.

Other

- *Discounting* was switched off.
- *Time-frame* was set to 40 years. (that is, lifetime given the ages evaluated)

Assumptions regarding risk factor values:

- Risk factor values as given in the input table and the UKPDS Outcomes Model were translated into risk factor classes as is required for the MICADO model. The risk factor values were translated to the following risk factor classes:

Risk factor	UKPDS OM Risk factor value	MICADO Risk factor class	MICADO Risk factor class definition
Smoking status	Non-smoker (never)	1	Never smoker
	Smoker	2	Current smoker
Systolic blood pressure	140 mmHg	7	140-160 mmHg
Total cholesterol*	4.8 mmol/L	5	<5 mmol/L
	6.0 mmol/L	6	5-6.5 mmol/L

	7.2 mmol/L	7	6.5-8 mmol/L
	8.4 mmol/L	8	>8 mmol/L
	9.6 mmol/L	8	>8 mmol/L
BMI	27.1 – 29.8 kg/m^2	2	25-30 kg/m^2
HbA1c	6%	1	<6.5%
	8%	5	8-8.5%
	10%	8	>9.5%

*Total cholesterol was used as input instead of the Total:HDL ratio

- We assumed *no medication* use when choosing the risk factor classes. That is, levels of bloodpressure and cholesterol were by assumption obtained without use of statins or antihypertensiva
- *Risk factors were kept constant* over time by forcing the risk factor transition rates to zero.

Assumptions regarding outcome definition

For each example patient, a cohort of 1000 identical individuals was run through the model, after which outcomes were calculated.

Life expectancy (LE) is defined as the number of person-years lived by the cohort, divided by the initial population number.

Quality Adjusted Life Expectancy (QALE) is defined as the person-years lived in each state times the QALY weight for that specific health state, divided by the initial population number.

Complication incidence

- Cumulative incidence is defined as the sum of the incidence over a life-time (40 years) for all people, divided by the initial population number.
- Incidence rate is defined as the sum of the incidence over a life-time (40 years) for all people, divided by the number of person-years lived by the total population.

Macrovascular complications: Instead of the MI incidence we report only the Acute MI (AMI) incidence. Overall CVD in MICADO is defined as the sum of AMI, stroke, Congestive Heart Failure (CHF), and other Coronary Heart Diseases (mostly Angina Pectoris).

The following table defines these complications, that were based on GP registries using ICPC.

Condition	ICD-9	ICD-10	ICPC	ABREVIATION in MODEL	
Diabetes	250	E10-E14	T90	DM	
Heart- failure	428	I50	K77	CHF	
Coronary Heart Disease	410-414	I20-I25	K74-K76	CHD	(split into AMI+other CHD)
Stroke	430-438	G45, I60-I69	K89-K90	CVA	

Michigan Model for Diabetes

Assumptions made by the Michigan Modeling Team included:

1. DBP = 80
2. No one lived past 100 years of age.
3. Constant risk covariates (BMI, BP, Lipids, etc.) per instructions
4. All other model assumptions were based on the default values for the Michigan Model for Diabetes. Full documentation is available at: http://diabetesresearch.med.umich.edu/peripherals/DiseaseModel/MDRTC%20Diabetes%20Model/UserManual_MichiganModel_for_Diabetes_ver2.pdf
5. In particular, for QALYs we used health utility scores reported by Coffey et al. (2002) shown below in Table 1. These diabetes-specific health utilities are generally lower than those from the EQ-5D, for example. As such, we

would expect our utility scores to be lower than for models using other measures.

References:

Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH: Valuing health related quality of life in diabetes. Diabetes Care 25:2238–2243, 2002.

Table 1. QWB-SA utility scores in the Michigan Model for Diabetes (MMD) and EQ-5D utility scores from UKPDS 72 (Clarke, 2005) or UKPDS 62 (Ref #16 in UKPDS 72)

Disease status	Complication level	MMD	EQ-5D from UKPDS 72 or UKPDS 62 (Ref #16 in UKPDS 72)	
		QWB-SA	EQ-5D from UKPDS 72	EQ-5D from UKPDS 62
	Intercept	0.689	0.79	0.785
Sex	Male	(Ref)		
	Female	-0.038		
BMI (kg/m^2)	Obese (BMI ≥30)	-0.021		
Diabetes Intervention	None or diet only	(Ref)		
	Oral/non-insulin agents	-0.023		
	Insulin	-0.034		
Retinopathy	Both eye are not blind	(Ref)	(Ref)	(Ref)
	Non-proliferative retinopathy	-0.000		
	Macular edema or proliferative retinopathy	-0.000		
	Blind in one eye	-0.043	-0.07	-0.074
	Blind in two eyes	-0.170		
Nephropathy	No nephropathy	(Ref)		

	Microalbuminuria or proteinuria	-0.011		
	ESRD dialysis	-0.078	???	Insufficient
	ESRD transplant	-0.078		Events
Neuropathy	No neuropathy	(Ref)	(Ref)	(Ref)
	Clinical neuropathy	-0.065		
	Amputation	-0.105	-0.28	-0.280
Cerebrovascular disease	No stroke	(Ref)	(Ref)	(Ref)
	Stroke	-0.072	-0.16	-0.164
Cardiovascular disease	No CHD	(Ref)	(Ref)	(Ref)
	Angina (other CHD w/o MI)	-0.026†	-0.09	-0.090
	MI	-0.026†	-0.06	-0.055
	PTCA	-0.026†		
	CABG	-0.026†		
	CHF	-0.052	-0.11	-0.108
High blood pressure	High BP or on BP meds	-0.011		

†Coffey et al. (2002) did not provide a penalty for having history of Angina or MI/PTCA/CABG. In Zhang et al. (2012), the penalty for other heart disease is approximately half of the penalty for CHF. We therefore imputed the penalty for Angina and MI/PTCA/CABG as half of the penalty for CHF.

MMUs Diabetes Model

1. General

The MMUs Diabetes Model is a probabilistic discrete-time model with a fixed cycle of 1 year. The equations reported in the UKPDS Outcome Model (UKPDS 68; Clarke et al, 2004) were used to predict probabilities of diabetes-related complications and mortalities.

Diabetes-related complications include: ischemic heart disease (IHD), acute myocardial infarction (AMI), congestive heart failure (CHF), ischemic stroke (STROKE), amputation(AMP), blindness in one year (BLIND) and renal failure (RENAL).

Mortality include: death in the first year following the first occurrence of a complication that increases the risk of mortality, which is AMI, CHF, STROKE, AMP or RENAL; diabetes-related mortality of patients with a history of any of the fatal complications; and death from causes unrelated to diabetes.

2. Model inputs

The equations used to calculate probabilities of complications and mortalities are functions of one or more of the following risk factors: age, gender, ethnicity, smoking status, BMI at diagnosis of diabetes, glycated hemoglobin (HbA1C), systolic blood pressure (SBP), ratio of total cholesterol to high-density lipoprotein (TOT2HDL), atrial fibrillation (ATRFIB) at diagnosis of diabetes, peripheral vascular disease (PVD), at diagnosis of diabetes and history of each of the diabetes-related complications. Inputs for these risk factors are provided in Table 1.

Table 1. Model inputs for the 2016 Mt Hood Challenge 2

Variable	Definition	Value at the start of the simulation	Time-dependent?
AGE_DIAG	Age at diagnosis of diabetes (years)	60	No
AGE	Current age	65	Yes
AGE_EVENT	Age at the cycle when the first occurrence of any of the complications that increase risk of mortality	NA	Yes
FEMALE	Indicator of female gender; 1 = female; 0 = male	0 or 1	No
ETHN	Indicator of ethnic groups; 1 = Afro-Caribbean; 0 = Caucasian or Asian Indian	1	No
SMOKE	Smoking status; 0 = never smoker; 1 = past smoker; 2 = current smoker	0 or 2	No
BMI_BASE	Body mass index at diagnosis of diabetes (m/kg^2)	29.8 if FEMALE = 1; 27.6 otherwise	No
HbA1C	Glycated hemoglobin (%)	6, 8 or 10	No
SBP	Systolic blood pressure (mm Hg)	140	No
TOT2HDL	Total cholesterol : high-density lipoprotein	4, 5, 6, 7 or 8	No
ATRFIB	Indicator of the presence of ATRFIB at	0	No

	diagnosis of diabetes; 1 = presence; 0 = absence		
PVD	Indicator of the presence of PVD at diagnosis of diabetes; 1 = presence; 0 = absence	0	No
IHD	Indicator of history of IHD; 1 = having a history; 0 = no history	0	Yes
AMI	Indicator of history of AMI; 1 = having a history; 0 = no history	0	Yes
AMI_EVENT	Indicator of the occurrence of first AMI within the current year; 1 = occurrence; 0 = no occurrence	0	Yes
AMI_POST	Indicating if the current year is after the year within which the first AMI occurred; 1 for all years after the year of event; 0 otherwise	0	Yes
CHF	Indicator of history of CHF; 1 = having a history; 0 = no history	0	Yes
STROKE	Indicator of history of STROKE; 1 = having a history; 0 = no history	0	Yes
STROKE_EVENT	Indicator of the occurrence of first STROKE within the current year; 1 = occurrence; 0 = no occurrence	0	Yes
STROKE _POST	Indicating if the current year is after the year within which the first STROKE occurred; 1 for all years after the year of event; 0 otherwise	0	Yes
AMP	Indicator of history of AMP; 1 = having a history; 0 = no history	0	Yes
BLIND	Indicator of history of BLIND; 1 = having a history; 0 = no history	0	Yes
RENAL	Indicator of history of RENAL; 1 = having a history; 0 = no history	0	Yes

3. Simulation specifications

For each unique set of values of input variables, the model created 10,000 patients with the same risk profile at baseline and tracked the occurrence of events during the remaining life time of the individual patients. For each patient, the simulation started at 5 years after diagnosis of diabetes (i.e. at the age of 65 years) and stopped when the patient died. Algorithm of the model simulation can be found in Clarke et al (2004).

4. Computations

4.1. Probabilities of diabetes-related complications

Proportional hazards Weibull regression was used in the UKPDS 68 to model hazard of the diabetes-related complications. The probability of an event occurring between time t and t + 1 is

$$1 - \exp\{H(t|x_{tj}) - H(t+1|x_{tj})\}, \quad (1)$$

where $H(t|x_{tj})$ is the cumulative hazard given a vector of risk factors at time t x_{tj},

$$H(t|x_{tj}) = \exp(\beta_0 + \beta_j x_{tj})t^{\Upsilon},$$

where $\lambda = \exp(\beta_0)$ and Υ are scale and shape parameters, respectively, in the Weibull distribution.

Specifically, the cumulative hazard of the diabetes-related complications considered in the present model was computed as follows:

$$H(t)_{IHD} = \exp\{-5.310 + 0.031*(AGE\_BASE - 52.59) - 0.471*FEMALE + 0.125*(HbA1C - 7.09) + 0.098*(SBP - 135.09)/10 + 1.498*LOG(TOTAL2HDL)\} * t^{1.150} \quad (2)$$

$$H(t)_{AMI} = \exp\{-4.977 + 0.055*(AGE\_BASE - 52.59) - 0.826*FEMALE - 1.312*ETHN + 0.346*SMOKE + 0.118*(HbA1C - 7.09) + 0.101*(SBP - 135.09)/10 + 1.190*LOG(TOT2HDL) + 0.914*IHD + 1.558*CHF\} * t^{1.257} \quad (3)$$

$$H(t)_{CHF} = \exp\{-8.018 + 0.093*(AGE\_BASE - 52.59) + 0.066*(BMI - 27.77) + 0.157*(HBA1C - 7.09) + 0.114*(SBP - 135.09)/10\} * t^{1.711} \quad (4)$$

$$H(t)\ STROKE = \exp\{-7.163 + 0.085*(AGE\_BASE - 52.59) - 0.516*FEMALE + 0.355*SMOKE + 0.128*(HBA1C - 7.09) + 0.276*(SBP - 135.09)/10 + 0.113*(TOTAL2HDL - 5.23) + 1.428*ATRFIB + 1.742*CHF\} * t^{1.497} \quad (5)$$

$$H(t)_{AMP} = \exp\{-8.178 + 0.435*(HbA1C - 7.09) + 0.228*(SBP - 135.09)/10 + 2.436*PVD + 1.812*BLIND\} * t^{1.451} \quad (6)$$

$$H(t)_{BLIND} = \exp\{-6.464 + 0.069*(AGE\_BASE - 52.59) + 0.221*(HBA1C - 7.09)\} * t^{1.154} \quad (7)$$

$$H(t)_{RENAL} = \exp\{-10.016 + 0.404*(SBP - 135.09)/10 + 2.082* BLIND\} * t^{1.865} \quad (8)$$

4.2. Probabilities of mortalities

The hazard of diabetes-related mortality and death from causes unrelated to diabetes was modelled in the UKPDS 68 using proportional hazards Gompertz regression. The probability of an event occurring between time t and t + 1 follows Equation (1) , where

$$H(t|x_{tj}) = \Upsilon^{-1} \{\exp(\Upsilon t) - 1\} \exp(\beta_0 + \beta_j x_{tj}), \quad (9)$$

where $\lambda = \exp(\beta_0)$ and Υ are scale and shape parameters, respectively, in the Gompertz distribution.

Specifically, the cumulative hazard of these mortalities was computed in the present model as follows:

$$H(t)_{DIABETES\ MORTALITY} = 1/0.003 * \{\exp(0.003*t) - 1\} * \exp\{-5.124 + 4.731*LOG(AGE\_EVENT) + 0.109*(TOTAL2HDL - 5.23) + 3.939*AMI\_EVENT + 1.119*AMI\_POST + 2.807*STROKE\_EVENT + 1.585*RENAL + 1.032*AMP\} \quad (10)$$

$$H(t)_{OTHER\ DEATH} = 1/0.154 * \{\exp(0.154*t) - 1\} * \exp\{-6.373 + 0.081*(AGE\_BASE - 52.59)*FEMALE + 0.104*(AGE\_BASE - 52.59)*(1 - FEMALE) + 0.307* SMOKE\} \quad (11)$$

The probability of mortality in the first year in which AMI, CHF, STROKE, AMP or RENAL occurs was modelled in the UKPDS 68 using the logistic regression, and was computed in the present model as

$$\frac{\exp\{-3.251 + 2.772 * \text{LOG(AGE\_EVENT)} + 0.114 * (\text{HbA1C} - 7.09) + 2.640 * \text{AMI\_EVENT} + 1.048 * \text{STROKE\_EVENT}\}}{1 + \exp\{-3.251 + 2.772 * \text{LOG(AGE\_EVENT)} + 0.114 * (\text{HbA1C} - 7.09) + 2.640 * \text{AMI\_EVENT} + 1.048 * \text{STROKE\_EVENT}\}} \quad (12)$$

4.3. Health utility

Based on study by Clarke et al (2002), health utility of a patient at the beginning of the simulation, i.e. one without a history of diabetes-related complication, was set at 0.78. When a complication occurs, the health utility was reduced using the following decrement: -0.090 for IHD, -0.055 for AMI, -0.108 for CHF, -0.164 for STROKE, -0.280 for AMP and -0.074 for BLIND. Decrement for renal failure was not reported in Clarke et al

(2002); for this, the decrement was set at -0.078 based on the study by Coffey et al (2002) in patients with type 2 diabetes and with nephropathy that needs a dialysis.

4.4. Quality-adjusted life years (QALYs)

When an event occurs, we assume that it occurs as the end of a cycle and that health utility changes linearly from the time point of the preceding event or at the beginning of the simulation (if no event had occurred) to the time point of the current event. QALYs corresponding to the period between these two time points were calculated as the area under the utility line.

References

Clarke, P.M., Gray, A.M., Briggs, A., Farmer, A.J., Fenn, P., Stevens, R.J., Matthews, D.R., Stratton, I.M., Holman, R.R. and UK Prospective Diabetes Study (UKPDS) Group, 2004. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia*,*47*(10), pp.1747-1759.

Clarke P, Gray A, Holman R (2002). Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPS 62). Med Decis Making 22:340-349.

Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH (2002). Valuing health-related quality of life in diabetes. Diabetes Care 25:2238-43.

SPHR Diabetes

Model approach

The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care costs under alternative scenarios for diabetes prevention. A wide range of stakeholders were involved in its development including clinicians, public health commissioners, diabetes and health economic researchers and members of the public with diabetes.

The model is an individual patient simulation model. The model was designed to include personalised trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP), cholesterol and measures of blood glucose (including HbA1c). However, since most of these risk factors were required to remain constant in this challenge, the evolution of these trajectories was not modelled in the base case and metabolic factors were assumed to remain constant. In addition, the model can incorporate both intentional screening and opportunistic detection and treatment for diabetes, high cardiovascular risk and hypertension. However, since everyone in the population was assumed to have diabetes at baseline, and their cholesterol and blood pressure levels were set and unvarying, no diagnosis or treatment effects were therefore modelled in the base case.

The model perspective is that of the NHS and Personal Social Services (PSS). In accordance with the challenge specification, the model had a lifetime horizon, and no discounting was applied.

Population

The baseline population was provided by the organisers and included one individual in each of 55 subgroups as defined by sex (Male/Female), smoking status (Never/Current), Total:HDL cholesterol ratio (4.0/5.0/6.0/7.0/8.0mmol), LDL cholesterol (2.5/2.85/3.3/4.0/5.0 for males , 3.0/3.4/34.0/4.8/6.0 for females) and HbA1c (6.0/8.0/10.0%). There were no population weightings and all individuals had the following fixed characteristics: age (65), systolic blood pressure (140 mmHg), weight (84kg if male, 90kg if female), height 1.74m (therefore fixed BMI by sex), HDL cholesterol (1 mmol if male, 1.2mmol if female), diabetes (diagnosed) for 5 years, no pre-existing cardiovascular or diabetes-related events, vascular disease or atrial fibrillation.

The baseline population provided also specified a series of characteristics that are not explicitly modelled in the SPHR diabetes model. This includes eGFR, heart rate, haemoglobin and white blood count, which are required in the UKPDS2 risk equations. Where the SPHR diabetes model uses these risk equations (for estimating retinopathy and neuropathy), the baseline hazard is adjusted to take account of the missing covariates (See appendix for full details). We assume a uniform value for them across all individuals based upon expected mean values reported by UKPDS (7). In this analysis we updated the values with the values provided for the Mount Hood Challenge. The baseline hazard for these risk equations was altered for the Mt Hood analysis to take account of the values given in the baseline population spreadsheet. Note that this method is unable to take account of differences between individuals, so where there were different values reported for males and females the mean of these two values was used instead.

Given that the SPHR diabetes model uses trajectories to estimate changes in metabolic risk factors over time, it is not simple to specify a change in risk factors occurring at a particular point in time. This means that the time-paths specified in the Mt Hood instructions (changes in BMI, eGFR, heart rate, haemoglobin and white blood count at year 10) could not be incorporated into the analysis. The SPHR diabetes model requires a number of characteristics for which data were not available in the dataset provided. The following assumptions were therefore made:

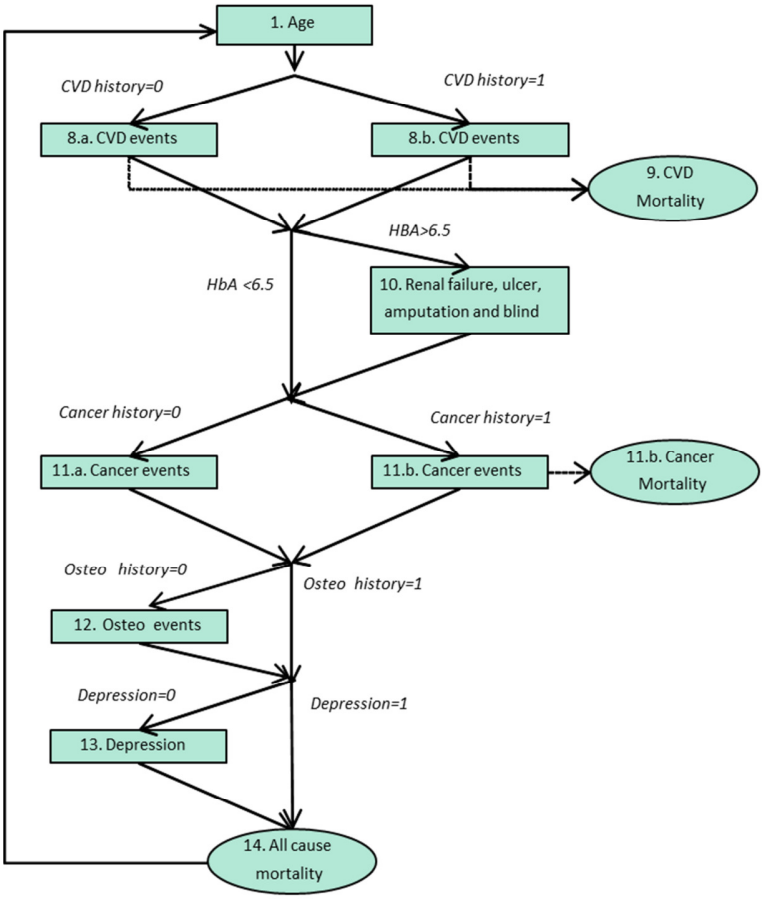
1. All individuals have a Townsend (area-based deprivation measure) score of 0
2. All individuals are economically active
3. All individuals have equal weighting (of 1)
4. All individuals are diagnosed diabetics on treatment, and have already benefited from any treatment effect.
5. EQ-5D is 0.7254 based on the estimate of mean EQ-5D for an individual with diabetes aged 65 from a published analysis of Health Survey for England data (8)
6. No individuals are receiving hypertension treatment or statins at baseline
7. No individuals have past CVD, anxiety, depression, renal disease, atrial fibrillation or rheumatoid arthritis
8. No individuals have family history of diabetes or CVD

Model procedure overview

Figure 1 illustrates the sequence of updating clinical characteristics and clinical events that are estimated within a cycle of the model. This sequence is repeated for every annual cycle of the model. The first stage of the sequence updates the age of the individual. In the second stage onwards the individual may experience cardiovascular outcomes, diabetes related complications, cancer, osteoarthritis or depression dependent on their risk factors. If the individual has a history of cardiovascular disease (CVD history=1), they follow a different pathway in stage eight to those without a history of cardiovascular disease (CVD history=0). All individuals with HbA1c >6.5% are assumed to be at risk of diabetes related complications. Individuals who do not have a history of cancer (Cancer history=0) are at risk of cancer diagnosis, whereas those with a diagnosis of cancer (Cancer history=1) are at risk of mortality due to cancer. Individuals without a history of osteoarthritis or depression may develop these conditions in stages 12 and 13. Finally, all individuals are at risk of dying due to causes other than cardiovascular or cancer mortality. Death from renal disease is included in the estimate of other-cause mortality.

The SPHR Diabetes Prevention Model allows a variety of different outcomes to be gathered including costs, life-years, quality-adjusted life-years (QALYs) and the number of events such as diabetes diagnoses or cardiovascular disease (CVD) cases.

Figure 2: Model schematic showing what happens in each yearly cycle.



Discussion

The results we are comparing with were taken from the original UKPDS outcomes model (it was subsequently updated in 2013). The UKPDS model includes the following risk factors: age, sex, race, smoking HbA1c, SBP and cholesterol ratio. The SPHR model includes additional risk factors as follows: area-based deprivation (Townsend score), economic activity, history of CVD, anxiety, depression, renal disease, AF or RA and family history of diabetes or CVD. To parameterize the SPHR model we assume all individuals have average deprivation, are economically active, and have no history or family history of family history or CVD and in doing so we are likely to be starting the model with a relatively low-risk population, compared with UKPDS (which included all diabetic individuals only excluding those with more than one vascular event or a severe co-morbidity).

The UKPDS model allowed key variables (HbA1c, SBP, cholesterol ratio and smoking status) to change over time, whereas for this comparison, we were required to hold all risk factors constant. This means that the older patients get in the model, the more their risk factors in UKPDS are likely to differ from the risk factors in the SPHR model, which are held at baseline.

Assuming risk factors generally get worse over time this is likely to have three effects:

- Lead to relatively lower incidence in the SPHR model because of comparatively lower risks
- Lead to bigger differences between outcomes between models in women than in men, as women live longer
- Lead to lower relative incidence in the SPHR model amongst non-smokers (since they can never become smokers) and higher incidence amongst smokers (since they can never become non-smokers)

However, the UKPDS risk factors are taken from a trial of blood glucose management, and therefore incorporate a short-term treatment effect which reduces risk. Patients in the SPHR model are assumed to have already been diagnosed and treated for diabetes and therefore gain no benefit from a treatment effect.

The UKPDS model includes the following outcomes: MI, other IHD, stroke, CHF, amputation, blindness and renal disease. In addition to this, the SPHR model includes outcomes for osteoarthritis and depression (QoL effect) and cancer (QoL and mortality effect). As a result, the SPHR model will include additional incidence of these conditions, leading to a greater QALY loss than in the UKPDS results, and a greater risk of death from cancer than is captured in the 'other causes' mortality in the UKPDS.

The UKPDS model is based on a diabetic population, therefore, all individuals are liable for diabetic complications. In the SPHR model, diabetes complications and increased mortality are assumed to apply only to those with HbA1c greater than 6.5%. Therefore, those with HbA1c of 6.0% do not accrue any complications or additional deaths in our results, leading to lower QALY and LE effects in the SPHR model.

Some of the effects in the SPHR model were taken directly from the UKPDS study (including risk of diabetes complications, and utilities for all events except renal failure and foot ulcers) so we would expect these effects to be very close to the UKPDS model. However, the SPHR model measure of CVD risk was based on the QRISK2 equations, which is based on a population of both diabetic and non-diabetic individuals and is more recent (1993-2008). The use of QRISK to calculate CVD risk may lead to a reduced overall incidence in comparison to UKPDS as the study potentially takes into account more recent advances in management of patients which reduces their overall risk.

The published and provided UKPDS outcomes do not include individual events, so we were unable to compare all these outcomes. However, we were able to compare overall life expectancy estimates. Overall, the SPHR model produced higher estimates of LE in all subgroups than did the UKPDS for the matched subgroup (from 7% to 45% longer LE). The difference is greater in the higher risk groups (greater HbA1c, greater cholesterol ratio, smokers).

This likely reflects the effects described above, namely:

- The use of a slightly healthier modelled starting population

- The absence of worsening risk factors over time
- The use of more recent CVD risk estimates, reflecting improvements in management

However, there will have been a small attenuation in the difference in overall life expectancy due to the inclusion of two specific additional cancer mortality risks in our model.

The example results shown here are not fully representative of the SPHR model outcomes, since the SPHR model was designed to allow lifetime trajectories of risk factors to be followed by individuals in the population. Because of the design of the challenge, risk factors were instead held constant. It also allows for the effects of screening and treatment of related conditions (hypertensions and hyperlipidaemia) to be modelled in the population over time, which again was removed from the model when generating these challenge results.

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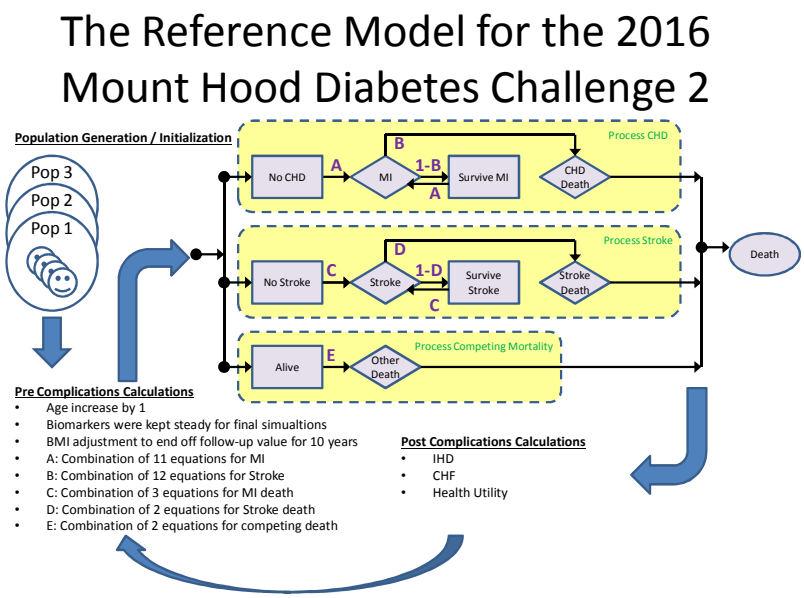
The Reference Model

The Reference Model advanced has been documented in other sources. For this exercise, population generation was mostly dictated, so modeling assumptions are minor there. The only element that seemed of importance regarding population generation is the year the data is associated with. This parameter is relevant to how much the model is corrected in temporal correction. Since no information was provided it was assumed that the data was generated in the years 1996 to 2010.

Amputation was not modeled as an active components and retinopathy was not modeled. Health utility was defined by UKPDS 72. CVD definition is simplified including only MI and Stroke.



For this exercise there were two simulation stages:

1. **Optimization Stage:** In this stage the assumption engine figures out the best model combination mixture to fit known outcomes from multiple studies. The studies were: ASPEN, ADVANCE, ACCORD, UKPDS, KP, NDR, Look AHEAD, ADDITION, CARDS. The optimization technique is reported in [2]. In this case 11 MI equations, 3 MI death equations, 12 stroke equations, 2 stroke death equations and 2 competing mortality equations were optimized together. The best model that did not rely on change of biomarkers was selected.
2. **Simulation Stage:** In this stage the best model mixture extracted by the optimization stage was executed over a base population that varies the parameters of interest. 960 simulations were conducted each time simulating a different combination of parameters to build the final table. Each simulation consisted of 1000 individuals and repeated 10

times to reduce the Monte-Carlo error. Results were collected and analyzed using python scripts.

These two stages were completed twice for two different scenarios with the following assumptions:

1) Without temporal correction of equations
2) With temporal correction of equations

The latter scenario assumes the models get old as medical practice improves in time. Therefore, the latter scenario adds a correction element to correct older MI and Stroke equations to fit newer or older data. In both cases competing mortality is left the same.

The gaps between the two simulations are analyzed below.

Gaps

The spreadsheets below show the summary results for both models for ages 45,55 as initially requested before changing the challenge definitions to deliver a single 65 age parameter.

Since one result set was requested as results, the choice was to submit the optimistic future model that is corrected for medical practice improvement since it had a better fitness to data. The models in the two scenarios had significant difference in equation combinations and emphasized different equations.

It is clear that the assumption that corrects models for improvement in medical practice improves lifespan significantly. Considering all cells the improvement mean is 7 years, min = 3.6 years, max = 11.8 years difference.

Even a quick look at the heat maps reveals also that the model with the temporal correction is more sensitive to age than other parameters.

However, it is important to remember that the assumption is that the population sampled from 1996 to 2010 which is past the time UKPDS conducted its study. This is a major factor than needs attention and may change results significantly for a different data timestamp. Due to lack of time no sensitivity analysis was conducted to see the effect of time.

Although the model with temporal correction had better fitness to the studies it was compared to, it is important to remember that the assumption is that medical improvement rate will continue at the same pace as observed. If models assumptions are true, we are looking at a much brighter future. However, if medical practice will improve less, the model without temporal correction may prove more descriptive of the future.

A comparison was made of both scenarios to the 55 age group in figure 1 provided in [1] using the UKPDS outcomes model. It is apparent that both scenarios are optimistic compared to the published numbers. The model in the first scenario was much closer to the results in [1]. The

simulations conducted hold information that will allow full comparison of the matrix for the 65 and 75 age groups as well, yet due to the short time and unavailability of reference data in spreadsheet form it was not conducted.

The 65 age population with 140 BP that was requested in the final result form had significant differences from the numbers in figure 1 in [1]. It provides a much higher life expectancy to clearly sick people. However, do recall that this is an optimistic model assuming that medical practice will continue at the observed rate of continuous improvement. Considering new efforts with medical devices, models, and accumulation of medical knowledge in Electronic Medical Records (EMR), that can improve treatment and prevention in the future, this assumption seems reasonable.

Reproducibility Information:

The results for this challenge were calculated on a 16 core cluster with 5 nodes running Ubuntu 12.04 Linux using Sun Grid Engine and Python 2.7.8 deployed by Anaconda 2.0.1 (64-bit). Results were generated using MIST version (0,94,2,0) with Inspyred version 1.0. The simulations, including random seed are archived under the following files:

Original model mixture:

> Optimization Run: MIST_RefModel_2016_05_20_OPTIMIZE.zip using model version 34
>
> Simulation Run: MIST_RefModel_2016_06_26_MH2016_Challenge2.zip using model version 36

Mixture of models with temporal correction:

> Optimization Run: MIST_RefModel_2016_08_07_OPTIMIZE.zip using model version 34
>
> Simulation Run: MIST_RefModel_2016_08_18_MH2016_Challenge2.zip using model version 36

Additional python scripts were needed to recalculate QALYS and assemble the reports. Those scripts are archived in the files:
MH2016_Ch2_1_Correcting_MIST_RefModel_2016_06_26_MH2016_Challenge2.zip and

MH2016_Ch2_2_Correcting_MIST_RefModel_2016_08_18_MH2016_Challenge2.zip

References:

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UKPDS Outcomes Model

Inputs/assumptions:

- We used the excel spreadsheet as provided to simulate the different outcomes of the challenge. We made no additional assumptions nor required further data.
- We allowed for 70 years of simulation which was sufficient to cover the expected life-time of the 65 year old population.
- Modifiable risk factors (SBP, smoking, HbA1c, LDL and HbA1c) were held constant. Other risk factors (white blood cell count, eGFR, BMI, heart rate, and haemoglobin) were simulated as provided in the excel spreadsheet (i.e. changing every 10 years).
- We used HDL to LDL ratio where HDL was fixed for all patients (1.2 for females and 1.0 for males based on UKPDS study data) and LDL was changed to match the desired ratios.
- To estimate QALYs we used UKPDS utilities from Alva et al. (2013).
- No discounting was applied to (quality-adjusted) life expectancy.
- Complications are reported as cumulative incidence and refer only to first events (number of first events divided by initial sample size). Second events of the same complication are not accounted for in the estimates provided. For example, second MIs do not contribute to MI cumulative incidence.
- The number of Monte-Carlo simulations (inner loops) per patient simulated was set at 100,000. The reported values per cell of risk were obtained by averaging the 100,000 simulations.
- We did not simulate parameter uncertainty.

References:

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. 2013:10.