Economics, Simulation Modelling and Diabetes: Mount Hood Challenge 2022

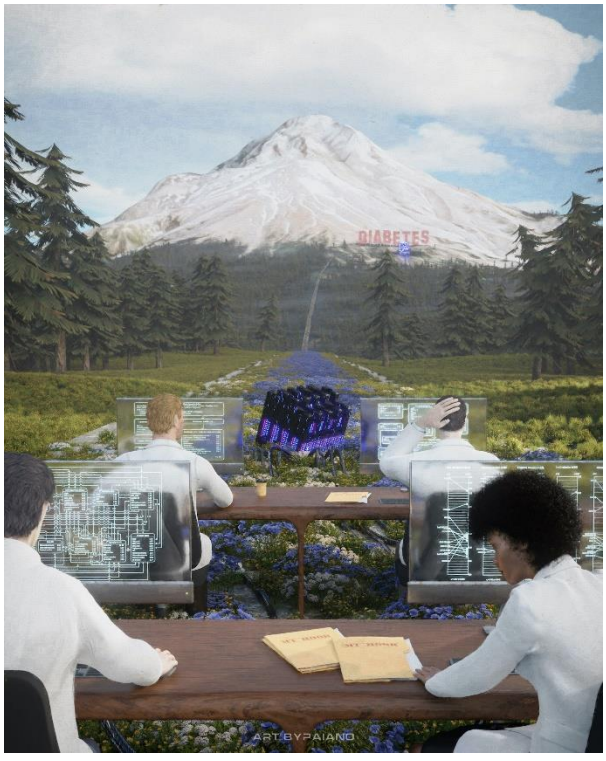
Clinical Research Centre,

Jan Waldenströms gata,

University of Lund,

Malmo, Sweden

24th September 2022



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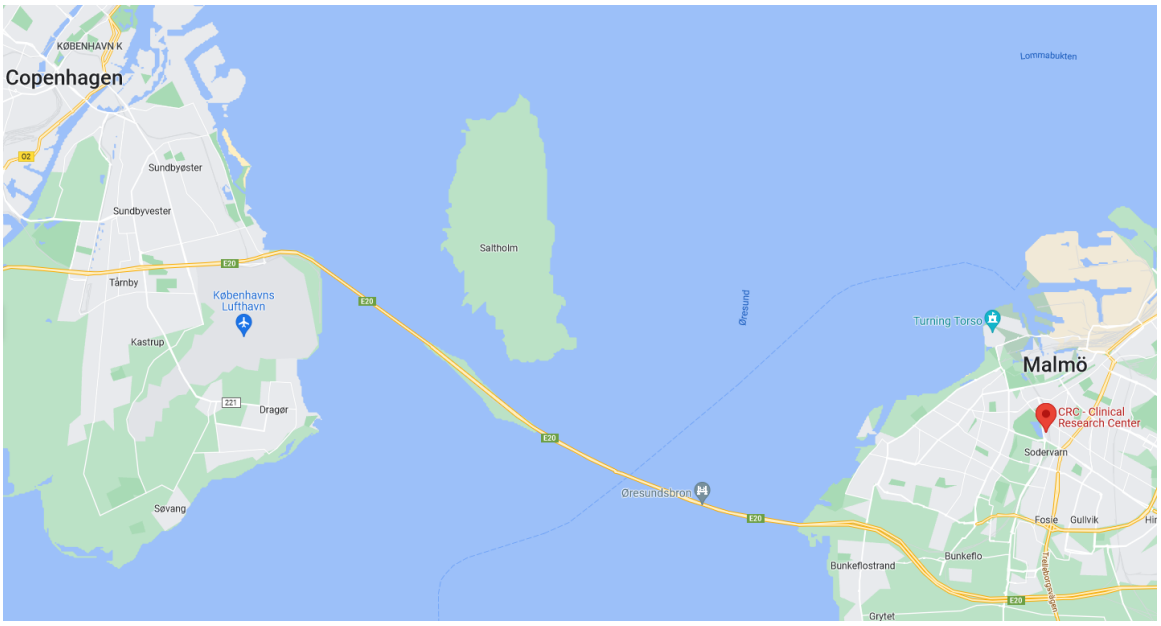
Conference Centre Map and General Information

Location: The conference will be held at the Clinical Research Center, Jan Waldenströms gata 35, 205 02 Malmö, Sweden.



Registration for the conference will be from 8:30am onwards on Saturday, 24th September. The conference will conclude at 5pm, with the Mount Hood Business meeting following from 5-6pm.

Conference registration includes lunches/refreshments and a conference dinner on the evening of 24th September.

Conference Dinner

The conference dinner will be held at the Clarion Hotel Malmö Live. Further detail will be provided on the day.

Mount Hood Organising Committee 2022

Philip Clarke, University of Oxford & University of Melbourne

Jose Leal, University of Oxford

Phil McEwan, Health Economics and Outcomes Research Ltd

Andrew Palmer, University of Tasmania

Michael Willis, Swedish Institute for Health Economics

Josh Knight, Statistically Speaking

James Altunkaya, University of Oxford

The organising committee is chaired by Professor Philip Clarke, University of Oxford and this year's conference is being hosted by Professor Katarina Steen Calsson & Dr Michael Willis of the Swedish Institute for Health Economics (IHE).

Thanks are due to:

Katarina Steen Carlsson, Gunhild Anderson, Mike Willis, Andreas Nilsson as hosts and local organisers; Jose Leal, Philip Clarke, Mike Willis, Phil McEwan, Andrew Palmer and Mark Lamotte on developing the challenges; Josh Knight for co-ordinating registration and programme administration; and James Altunkaya for compiling the programme and challenge results.

List of Participants

Amanda	Adler	Diabetes Trials Unit, University of Oxford
James	Altunkaya	Health Economics Research Centre, University of Oxford
Hamza	Alshannaq	DexCom
Gunhild	Anderson	Swedish Institute for Health Economics
Timothy	Arnaut	Roche
Douglas	Barthold	University of Washington
Sasha	Berry	Novo Nordisk
Gunnar	Bradvik	Swedish Institute for Health Economics
Jonathan	Briody	University College Dublin
Barnaby	Cheadle-Hunt	Ossian Consulting
Philip	Clarke	Health Economics Research Centre, University of Oxford
Ruth	Coleman	Diabetes Trials Unit, University of Oxford
Talitha	Feenstra	University of Groningen
Volker	Foos	HEOR
Adam	Fridhammar	Swedish Institute for Health Economics
Luiza	Grazziotin	CADTH
Rodolfo	Hernandez	University of Aberdeen
Elbert	Huang	University of Chicago
Morten	Jensen	Novo Nordisk
Klas	Kellerborg	Swedish Institute for Health Economics
Shihchen	Kuo	University of Michigan
Neda	Laiteerapong	University of Chicago
Mark	Lamotte	IQVIA
Karen	Lee	CADTH
Amanda	Leiter	Mount Sinai
Xinyu	Li	University of Groningen
Jing	Li	University of Michigan
Peter	Lindgren	Swedish Institute for Health Economics
Samuel	Malkin	Ossian Consulting
Luis	Martins	IQVIA
Phil	McEwan	HEOR
Andreas	Nilsson	Swedish Institute for Health Economics
Andrew	Palmer	University of Tasmania
Sofie	Persson	Swedish Institute for Health Economics
Catrin	Plumpton	University of Bangor

Richard	Pollock-Wilkins	Ossian Consulting
Ryan	Pulleyblank	NHTA
Jianchao	Quan	Hong Kong University
Mafalda	Ramos	IQVIA
Hongye	Ren	Novo Nordisk
Wendelin	Schramm	Heilbronn University of Applied Sciences
Hui	Shao	University of Florida
James	Shearer	Kings College London
Harry	Smolen	Medical Decision Modelling
Katarina	Steen Carlsson	Swedish Institute for Health Economics
Zin Min	Thet Lwin	Swedish Institute for Health Economics
An	Tran-Duy	University of Melbourne
William	Valentine	Ossian Consulting
Michael	Willis	Swedish Institute for Health Economics
Aaron	Winn	Medical College of Wisconsin
Wen	Ye	University of Michigan

Pre-conference workshop

Diabetes and simulation modelling

23 September 2022 from 2pm to 5pm

3rd Floor, Swedish Institute for Health Economics (IHE), Råbygatan 2, 223 61 Lund, Sweden

Outline

Introduction to diabetes modelling

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

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

Costs of treatments and complications

- Changes in the price and expenditure of diabetes therapies: recent evidence
- Options for collecting resource use information
- Sources of costing data in other countries – Sweden, Australia, ADVANCE.

Future directions in modelling

- Adapting models across settings
- Calibration risk equations
- 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

The future of diabetes simulation modelling

- Capturing new treatments and interventions
- Can we develop a universal model?
- Software for simulation modelling

Speaker

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.

Economics, Simulation Modelling and Diabetes:
Mount Hood Challenge, Malmo 2022

Conference overview

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

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

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

Participation in publications arising from the meeting

In the past several groups participating in the conference have collaborated on a subsequent publication. Involvement in the publication process is on a voluntary basis and involves acceptance of the following principles:

i. No team can block publication of the paper except because of concerns related to scientific soundness — e.g., the data collection, analyses and presentation were done incorrectly. Concerns related to policy, management, or scientific implications are not grounds for a co- author to block publication. If a majority of Team members believe the paper should be published based on sound science, the paper will move forward. Every reasonable effort should be made by the Leader and others to reach a consensus on moving forward with a publication.

ii. Teams may voluntarily remove themselves from the project, and from co-authorship, at any point if they no longer have time for the project or they disagree with some aspect of the project or paper. If a Team voluntarily leaves the project or is asked to leave because they are opposed to the paper being published, the Team and Chair of Mt Hood Steering Committee will need to discuss with the dissenting member if his/her contributions can still be used, and perhaps described in the Acknowledgements, or if their contribution will have to be removed from the paper.

Economics, Simulation Modelling and Diabetes: Mount Hood Challenge 2022

Plenary Speakers

Professor Amanda Adler

Amanda Adler trained in economics, medicine, and epidemiology in the US, and pharmacovigilance in the UK. In 2019, she returned to Oxford University to lead the Diabetes Trial Unit, DTU. The DTU runs studies to address interventions related to diabetes and endocrinology to improve health and collaborates closely with the Health Economic Research Centre.

She chaired a Technology Appraisal Committee at the National Institute for Health and Care Excellence (NICE) for 12 years evaluating over one hundred drugs and devices across disease areas. With NICE, she chaired the committee addressing new models to evaluate and purchase antimicrobials, chaired the Clinical Guidelines for Newer Agents for Type 2 Diabetes and chaired the Quality Standard for Diabetes. She received an award for Distinguished Contribution to NICE at the Parliamentary ceremony celebrating NICE's 20th anniversary.

She chairs the World Health Organisation Technical Advisory Group for Diabetes. She sees patients who have diabetes in the NHS. She is a Commissioner on the Commission on Human Medicines (CHM) and chairs the CHM's Expert Advisory Group Cardiovascular, Diabetes, Renal, Respiratory and Allergy, and previously chaired the Medicines and Health Products Regulatory Agency's Expert Group on the Safety of Insulin. She sits on the National Diabetes Audit Partnership Board and an NIHR funding committee. She supports projects that set priorities under universal health coverage having worked with the UK government, NICE, International Decision Support Initiative, the World Bank, and Organisation for Economic Co-operation and Development (OECD). She is a Fellow of the Royal Statistical Society.

Professor Philip Clarke

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

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

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

Conference Program

Venue	*CRC - Clinical Research Center, Jan Waldenströms gata 35, 205 02 Malmö, Sweden*
8:30-9:00am	**REGISTRATION**
9:00-9:45am	**Welcome & Plenary –** "United Kingdom Prospective Diabetes Study – 40 years on" Prof Amanda Adler & Prof Philip Clarke, *University of Oxford*
9:45-10:00am	**Award of Mount Hood transparency prize** Prof Andrew Palmer*, University of Tasmania*
10:00-11:00am	**Morning abstract session** Session chair: Prof Neda Laiteerapong*, University of Chicago*

Presentations (10 minutes each)	**Presenter**
Non-Glycemic Benefits from the Use of SGLT2's in Type 2 Diabetes: An Exploratory Analysis	Harry J. Smolen, *Medical Decision modelling (MDM)*
Contrasting 4 different mortality predictions in patients with type 1 diabetes using the IQVIA Core Diabetes Model	Dr Luís Martins, *IQVIA*
The potential value of identifying type 2 diabetes subgroups for guiding intensive treatment: a comparison of novel data-driven clustering to guideline-based subgroups	Xinyu Li, *University of Groningen*
Established cardiovascular disease in people with type 2 diabetes: Hospital-based care, days absent from work and costs and scenarios for model-based analysis of broader implementation of guideline recommended treatment	Dr Sofie Persson, *Swedish Institute for Health Economics (IHE)*
Trends in all-cause mortality among adults with diagnosed type 2 diabetes in Malaysia: 2010 – 2019	Prof. Philip Clarke, *University of Oxford*

11:00-11:30am	**Morning Break**

11:30-1:00pm

Challenge 1 : Revisiting the Mount Hood reference case for Type 1 & Type 2 Diabetes

Chair: Mike Willis, *Swedish Institute for Health Economics (IHE)* & Prof Talitha Feenstra, *University of Groningen*

All modelling groups present a brief overview of their model

ASCEND - T2	IHE-DCM - T2
CARDIFF -T1 & T2	IQVIA - T1 & T2
CHIME - T2	MDM-TTM - T2
COSMO - T1	MICADO - T2
DOMUS - T2	PRIME - T2
ECHO - T1 & T2	UKPDS - T2

1:00-2:00pm — **Lunch**
(Plenary repeated for virtual participants)

2:00-3:30pm

Challenge 2 : Costs & Cost-effectiveness of common treatments for diabetes

Chair: Dr Phil McEwan, *HEOR* & James Altunkaya, *University of Oxford*

3:30-4:00pm — **Afternoon Break**

4:00-5:00pm

Afternoon abstract session

Session chair: Harry Smolen*, Medical Decision Modelling (MDM)*

Presentations (10 minutes each)	**Presenter**
Costs of major complications in people with and without diabetes in Tasmania, Australia	Prof. Andrew Palmer
Using QALYs as a measure of global prediction accuracy in simulation models for diabetes	Dr Helen Dakin
Estimating Time Paths Of Risk Factors Among People With Type 2 Diabetes And Health Gains From Risk Factor Management	Dr Ni Gao
New simulation model for evaluating cost-effectiveness of treatments for people with diabetes without previous cardiovascular disease	Mi Jun Keng
Development and Validation of a Microsimulation Model for Chronic Kidney Disease Progression in Type 2 Diabetes Patients in the United States: Michigan Model for Diabetes-Chronic Kidney Disease Model (MMD-CKD)	Dr Wen Ye

5:00-6:00pm — **Closing remarks & Mount Hood business meeting**

Instructions for presenters in abstract sessions

- The time allocated for presentation will be 10 minutes each. Allow a minimum of one minute per slide, preferably 2–3 minutes.
- A laptop computer and projector will be provided for your presentation, using Microsoft PowerPoint software. Both slides formats, 4:3 or 16:9, can be accommodated.
- Arrive at the meeting room before the session begins and contact the session convener for last-minute instructions or changes in the schedule.
- Please bring along your slides on a USB stick and load them onto the computer during the break before your session.
- During your presentation, state the purpose and objectives of the paper, the main concepts and results, and the conclusions. Avoid too much detail.
- Do not exceed the allocated time for your presentation.
- Presenters will be given an opportunity to make a pdf of a paper or slides available on the conference website.

Abstracts (in order of presentation)

Non-Glycemic Benefits from the Use of SGLT2's in Type 2 Diabetes: An Exploratory Analysis

Dan Murphy[1], James Gahn[1], Xueting Yu[1], Harry Smolen[1]

[1]Medical Decision Modeling Inc.

Presenter Harry J. Smolen

Introduction Recent literature has focused on the cardiovascular disease (CVD) benefits of using sodium-glucose co-transporter 2 (SGLT2) inhibitors in the treatment of Type 2 diabetes (T2D). This study explored the cost effectiveness impact of one SGLT2 treatment, dapagliflozin, on CVD in T2D using the Treatment Transitions Model (TTM), a generalized cost-effectiveness microsimulation model for T2D. The analysis performed a 5-year extrapolation of treatment costs, medical costs, and clinical effects associated only with the CVD impact of the treatment.

Methods Data was from Wiviott et al., NHANEs and other literature. We opted to remove any treatment related clinical benefit related to dapagliflozin to avoid any potential double counting the treatment effect on CVD as we applied trial rate adjustments to TTM (UKPDS 82-based) for MI, stroke, and CHF events that implicitly include these clinical benefits. The analysis assumed complication rate reductions due to treatment occurred throughout the 5-year analysis horizon. We also assumed the placebo arm as an anti-diabetic regime with treatment cost equal to the SLGT2 arm.

Results Accounting for only CVD-related impacts, patients in the simulated dapagliflozin arm saved $773 over five years compared to the placebo arm. The primary drivers of this savings were reductions in medical costs for CHF ($433) and MI ($446) against an increased treatment outlay of $50.78. Case reductions for new CHF and MI were estimated at 8.59 and 8.48 per 1,000 patients accounting for the CVD benefit of SGLT2 alone.

Conclusion The main drivers of SGLT2 CVD benefit from the TIMI–58 trial are reductions in CHF and MI. These results are not as impressive as some other trials but do offer a conservative value message that these CVD benefits can provide meaningful value for SGLT2. Finally, there is likely additional value from both weight loss and slowing renal eGFR loss.

Contrasting 4 Different Mortality Predictions In Patients With Type 1 Diabetes Using The Iqvia Core Diabetes Model

Authors: Martins L, Ramos M, Lamotte M

Objectives In modelling exercises, all-cause mortality is generally built up from disease and non-disease specific mortality data, where the latter is country specific general mortality that excludes disease specific mortality to avoid double counting (=non-specific mortality, NSM). The patients with type 1 diabetes (T1D) modelled tend to be young, so a reliable long-term prediction is crucial. In the IQVIA Core Diabetes Model (CDM), 4 mortality prediction approaches can be used: 1) the classical combination of diabetes specific mortality related to cardiovascular and microvascular complications combined with NSM ("non-combined mortality approach", NCMA), 2) the UKPDS 68 approach applying NSM and its specific equations, 3) UKPDS 82 approach fully based on its mortality risk equations, and the 4) West Australian approach using T1/2D specific equations. UKPDS approaches are determined from patients with type 2 diabetes. We aimed to assess the validity of the 4 approaches in patients with T1D compared to published data.

Methods Using the different mortality approaches, CDM9.5Plus analyses were conducted for a T1D cohort of average age of 27 years and 6 years of diabetes. Several HbA1c levels without progression over time were tested. Pittsburg cardiovascular risk equation was chosen. UK NSM was applied. The predicted 70-year survivals were compared against each other, but also against the findings of 2 publications (Pittsburg-Miller et al 2012; Australia-Huo et al 2016; same age and diabetes duration).

Results Both publications reported a median survival between 68 and 73 years. For modelled patients at the age of 70 years, survival was 1)52% 2)60% 3)44% 4)67%, as per mortality approach chosen. The NCMA approach has similar survival compared with the long-term studies.

Conclusions The use of the NCMA approach results in reliable predictions of long-term survival in patients with T1D. It accounts for changes in the management of diabetes and general healthcare.

The potential value of identifying type 2 diabetes subgroups for guiding intensive treatment: a comparison of novel data-driven clustering to guideline-based subgroups

Xinyu Li[1], Anoukh van Giessen[2], James Altunkaya[3], Roderick C. Slieker[4,5,6], Joline WJ Beulens[4,5,7], Leen M. 't Hart[4,5,6,8], Ewan R. Pearson[9], Petra J. M. Elders[5,10], Talitha Feenstra[1], Jose Leal[3]

[1] University of Groningen, Faculty of Science and Engineering, Groningen Research Institute of Pharmacy, Groningen, The Netherlands

[2] Centre for Nutrition, Prevention and Health Services, National Institute of Public Health and the Environment, Bilthoven, The Netherlands

[3] Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, UK

[4] Department of Epidemiology and Data Sciences, Amsterdam University Medical Center, location VUmc, Amsterdam, The Netherlands

[5] Amsterdam Public Health, Amsterdam, The Netherlands

[6] Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

[7] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

[8] Department of Biomedical Data Sciences, Section Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

[9] Division of Population Health and Genomics, Ninewells Hospital and School of Medicine, University of Dundee, Dundee, Scotland, UK

[10] Department of General Practice, Amsterdam University Medical Center, Location VUMC, Amsterdam, The Netherlands

Presenter name: Xinyu Li

Financial support: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement number 115881 (RHAPSODY). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation programme. The opinions expressed and arguments employed herein do not necessarily reflect the official views of these funding bodies.

OBJECTIVE To estimate the impact on lifetime health and economic outcomes of different methods of stratifying patients with type 2 diabetes and intensifying treatment, and to explore the impact of targeting cholesterol levels and BMI in addition to HbA1c in treatment intensification.

RESEARCH DESIGN AND METHODS We divided 2,935 newly diagnosed patients from the Hoorn Diabetes Care System cohort into five novel data-driven subgroups (based on age, BMI, HbA1c, C-peptide and HDL) and four guideline-based subgroups using HbA1c and risk of cardiovascular disease. The UKPDS Outcomes Model 2 estimated discounted lifetime complication costs and quality-adjusted life-years (QALY) for each subgroup and across all patients. Gains from treatment intensification were compared to "care-as-usual" and expressed in incremental QALYs and costs.

RESULTS Under care-as-usual, data-driven subgroups ranged from 7.9 and 12.6 QALYs (9.1 and 9.7 QALYs after age-sex-standardization). Guideline-based subgroups, ranged from 6.8 and 12.0 QALYs (8.7 and 9.6 QALYs after age-sex-standardization), and better discriminated differences in health outcomes. Two stratification methods followed by treatment intensification did not differ significantly in QALY gains and cost-savings. At $100,000 per QALY, identification and intensive glucose control treatment could cost $58-$368 per year and be cost-effective. Targeting BMI and LDL additionally to HbA1c could cost $799-$2578 per year and be cost-effective.

CONCLUSIONS Both classification methods support priority setting for intensive treatment, but the guideline-based subgroups may better identify patients with the most potential to benefit from intensive treatment. Cholesterol and weight control showed a significant potential for benefit in intensification of diabetes management.

Established cardiovascular disease in people with type 2 diabetes: Hospital-based care, days absent from work and costs and scenarios for model-based analysis of broader implementation of guideline recommended treatment

Authors: Kristoffer Nilsson[1]; Emelie Andersson[1]; Sofie Persson[1,2,]; Kristina Karlsdotter[3], Josefin Skogsberg[3], Staffan Gustavsson[3], Johan Jendle[4]; Katarina Steen Carlsson[1,2]

1. The Swedish Institute for Health Economics, Lund, Sweden
2. Department of Clinical Sciences, Malmö, Health Economics, Lund University, Lund, Sweden
3. Boehringer Ingelheim AB, Stockholm, Sweden
4. Institute of Medical Sciences, Örebro University, Örebro, Sweden

Presenter: Sofie Persson, the Swedish Institute for Health Economics, email sofie.persson@ihe.se

Study funding: This research was supported by a grant from Boehringer Ingelheim to the Swedish Institute for Health Economics.

Background and aims: People with type 2 diabetes have increased risk established cardiovascular disease eCVD. The objective was to assess excess hospital-based care, work absence, and mortality for people with type 2 diabetes with and without eCVD in comparison to matched controls in Sweden for use in model-based scenario analyses of increased implementation of guideline recommended.

Materials and methods: The study used a Swedish database with longitudinal individual-level data (2007-2016) for 454,983 people with type 2 diabetes and their matched controls (5:1 on year of birth, sex, and region of residence). eCVD was defined as presence of coronary artery disease, stroke, amputation, periphery vascular disease, non-fatal cardiac arrest, or related interventions in 1997-2006. Regression analysis was used to attribute costs of hospital-based care and days absent from work (age <66 years) to eCVD. Mortality adjusted for age, sex, and educational level was analyzed using Cox proportional hazards. The IHE Cohort Model of Type 2 Diabetes was used for scenario analyses of increased implementation of guideline recommendations.

Results: Thirty percent (n=136,135) of people with type 2 diabetes were observed with eCVD in 2007-2016 (women 24%n=43,847; men 34% n=92,288). The mean annual costs of hospital-based care for diabetes complications were EUR 2,629 (95% CI 2,601 to 2,657) of which EUR 2,337 (95% CI 2,309 to 2,365) were attributed to eCVD (89%).

People with type 2 diabetes had on average 146 days absent (95% CI 145-147) of which 68 days (47%) were attributed to eCVD. Type 2 diabetes with eCVD had increased mortality risk with a hazard ratio 4.63 (95% CI 4.58 to 4.68) compared with controls without diabetes and eCVD. Preliminary results from scenario analyses of implementation will be shown.

Conclusion: The study shows the burden of eCVD in type 2 diabetes for the individual and for society and the health and budget impact of broader implementation of guideline recommended treatments.

Trends in all-cause mortality among adults with diagnosed type 2 diabetes in Malaysia: 2010 – 2019

Lee-Ling Lim[1,2,3], Alia Abdul Aziz[1], Helen Dakin[4], John Buckell[4], Yuan-Liang Woon[5], Laurence Roope,[4] Arunah Chandran[6], Feisul I. Mustapha[6], Edward W. Gregg[7], Philip M. Clarke[4*]

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[4] Health Economics Research Centre, Nuffield Department of Public Health, University of Oxford, Oxford, United Kingdom

[5] Centre for Clinical Epidemiology, Institute for Clinical Research, National Institute of Health, Selangor, Malaysia

[6] Non-communicable Disease Section, Disease Control Division, Ministry of Health, Putrajaya, Malaysia

[7] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

Background: In high-income countries, all-cause mortality among patients with type 2 diabetes mellitus (T2DM) has declined since 1990s but whether such positive trends have occurred in low- and middle-income countries is unknown.

Aims: To determine 10-year trends in mortality in patients with diagnosed T2DM in West Malaysia.

Method: One million patients aged 40-79 with diagnosed T2DM registered in the National Diabetes Registry (1 January 2009-31 December 2018) were linked to death records (censored on 31 December 2019). Standardised absolute mortality rates and standardised mortality ratios (SMRs) were estimated relative to the Malaysian general population. The SMRs and mortality rates were standardised to the 2019 registry population with respect to sex, age group, and T2DM duration.

Results: In both sexes, overall all-cause standardised mortality rates were unchanged over time. Rates increased significantly in males aged 40-49 (annual average percent

change [AAPC]: 2.46 [95% CI 0.42, 4.55]) and 50-59 (AAPC: 1.91 [95% CI 0.73, 3.10]), and females aged 40-49 (AAPC: 3.39 [95% CI 1.32, 5.50]). In both sexes, standardised mortality rates increased over time among those with 1) >15 years T2DM duration, 2) prior cardiovascular disease, and 3) Bumiputera ethnicity. In 2019, the overall SMR was 1.83 (95% CI 1.80, 1.86) for males and 1.85 (95% CI 1.82, 1.89) for females, being higher in younger age groups.

Discussion: There was little or no improvement in mortality for patients with T2DM in Malaysia and mortality has worsened in several groups. Addressing challenges in care delivery with follow-up actions can close the gaps.

Financial support

This work was funded by the Medical Research Council. The project was also supported by the UK-Malaysia Joint Partnership on Non-Communicable Diseases under the Malaysia Partnership and Alliances in Research (MyPAiR), funded by the Ministry of Education, Malaysia (Grant number: IF076-2019). PC, LR, HD was partly funded by the National Institute of Health Research (NIHR) Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Costs of major complications in people with and without diabetes in Tasmania, Australia

Authors

Ngan T.T. Dinh[1,2], Barbara de Graaff[1], Julie A. Campbell[1], Matthew D. Jose[3,4], John Burgess[3,5], Timothy Saunder[3], Alex Kitsos[3], Nadine Wiggins[1], Andrew J. Palmer[1]

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[2]Thai Nguyen University of Medicine and Pharmacy, Thai Nguyen University, Thai Nguyen, Vietnam.

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[4]Australia and New Zealand Dialysis and Transplant Registry, South Australia, Australia.

[5]Department of Endocrinology, Royal Hobart Hospital, Tasmania, Australia.

Background and aims: Diabetes is a costly disease that places a huge burden on the Australian healthcare system. Most of the costs related to diabetes are due to management of complications. In order to reduce the economic burden of diabetes, it is essential to identify complications that are the key cost drivers. Additionally, estimating medical costs of complications in people with diabetes will provide essential input data for economic models to identify cost-effective interventions. Our study aimed to estimate costs of diabetes complications in the year of first occurrence and the second year, and to quantify the incremental costs of diabetes versus non-diabetes related to each complication.

Materials and methods: In this matched retrospective cohort study, people with diabetes (n=45,378) were identified based on either diabetes diagnostic criteria or diagnostic codes from a linked dataset in Tasmania, Australia between 2004-2017. Using propensity score matching, each of them was matched on age, sex, and residential areas with two matched non-diabetes people obtained from the same dataset. Direct costs (including hospital, emergency room visits and pathology costs) were calculated from the healthcare system perspective and expressed in 2020 Australian dollars. The average-per-patient costs and the incremental costs in people with diabetes were calculated for each complication.

Results: For people with diabetes, first-year costs of complications were: dialysis $87,460 (95% CI 79,818, 95,366), lower extremity amputations $71,258 (65,969, 76,427), kidney transplant $50,031 (34,619, 68,791), non-fatal myocardial infarction $33,196 (31,761, 34,458), foot ulcer/gangrene $32,628 (29,671, 35,606), heart failure $30,752 (29,235, 32,517), ischemic heart disease $30,538 (28,219, 32,922), non-fatal stroke $30,035 (28,606, 31,750), kidney failure $28,534 (23,398, 35,349), nephropathy $23,990 (18,471, 31,485), vitreous haemorrhage $21,630 (14,655, 29,259), neuropathy $20,347 (18,577, 22,555), retinopathy $20,290 (15,368, 26,711), angina pectoris $17,730 (16,416, 19,187), transient ischemic attack $17,638 (15,929, 19,850), blindness/low vision $15,607 (10,584, 21,668). The second-year costs ranged from 19% (ischemic heart disease) to 73% (dialysis) of first-year costs. Complication costs were 115%-259% higher than in people without diabetes.

Conclusion: Costs of treating complications are higher for people with diabetes versus people without diabetes. Diabetes complication treatment required substantial healthcare resources, even after the first year of occurrence. Costly complications included renal complications (especially dialysis), foot complications (especially lower extremity amputation), and macrovascular complications (especially non-fatal myocardial infarction). Our results can be used to populate diabetes simulation models and will support policy analyses to reduce the burden of diabetes.

Using QALYs as a measure of global prediction accuracy in simulation models for diabetes

Helen Dakin,[1] Ni Gao,[1,2] José Leal,[1] Rury R. Holman,[3] An Tran-Duy,[4] Philip Clarke[1]

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Objectives: To evaluate the use of quality adjusted life years (QALYs) to compare performance across models and identify the most accurate model for economic evaluation and health technology assessment. QALYs relate directly to decision-making and combine mortality and diverse clinical events into a single measure using evidence-based weights that reflect general population preferences. By contrast, clinical composite events give equal weight to all included events and no weight to other events.

Methods: We simulated participants from both arms of the EXSCEL trial (n=14,729) using the software versions of the UK Prospective Diabetes Study Outcomes Model version 1 (UKPDS-OM1) and 2 (UKPDS-OM2). The EXSCEL trial compared exenatide with placebo with median 3.2 years' follow-up. Default UKPDS-OM2 utilities were used to

estimate undiscounted QALYs over the trial period based on the observed events and survival. These were compared with the QALYs predicted by UKPDS-OM1 and UKPDS-OM2 for the same period. We assessed model performance for QALYs using mean squared error (MSE), mean absolute error (MAE), bias (observed minus predicted QALYs), R^2 and Q^2 (1-MSE/standard deviation^2). Models with smaller MSE or MAE and higher R^2 or Q^2 are considered better. Q^2 captures both discrimination and calibration and is comparable between different endpoints and subgroups.

Results: UKPDS-OM2 predicted patients' QALYs more accurately than UKPDS-OM1 (MSE: 0.210 vs 0.253; Q^2: 0.822 vs 0.786). UKPDS-OM1 underestimated QALYs by an average of 0.150, compared with 0.127 for UKPDS-OM2. The accuracy in predicting QALYs was influenced primarily by the accuracy in predicting mortality rather than other events. Sensitivity analyses showed that the results were robust to changes in utilities, events, censoring methods or discounting.

Conclusions: QALYs were a useful measure of model performance that could be used to assess the validity and calibration of other diabetes models and models in other disease areas.

Estimating Time Paths Of Risk Factors Among People With Type 2 Diabetes And Health Gains From Risk Factor Management

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Background: Most diabetes simulation models utilise equations mapping out lifetime risk factor trajectories. Existing equations, using historic data or assuming constant risk factors,

however, tend to underestimate or overestimate complication rates. It is important that simulation models use appropriate time path risk factor equations to capture key complication rates accurately.

Aims: (i) Update UKPDS-OM2 risk factor time path equations; (ii) Estimate QALY gains using original and updated risk factor equations; iii) Compare QALY gains for reference case simulations using different risk factor equations.

Methods: Using contemporary EXSCEL and TECOS randomised trial data (n=28,608), we estimated dynamic panel models to estimate continuous risk factors (HDL-cholesterol, LDL-cholesterol, glycated haemoglobin, haemoglobin, heart rate, body mass index and systolic blood pressure); a two-step approach for estimated glomerular filtration rate; and survival analysis for peripheral arterial disease, atrial fibrillation and micro- or macro-albuminuria. UKPDS-OM2 derived lifetime QALYs were extrapolated over 70 years using historical and new risk factor equations. We replicated the Mt Hood reference simulation with both sets of risk factor equations, and with last observation carried forward.

Results: All predicted risk factors were within the 95% confidence intervals of observed values, suggesting good agreement between observed and estimated risk factor values. Using historical risk factor trajectories, trial participants would have accrued 9.84 QALYs, increasing to 10.44 QALYs using contemporary trajectories, suggesting modern diabetes risk factor management was associated with a gain of 0.59 QALYs. The reference case simulation for men suggested that the combined intervention gained 0.75 QALYs using historical risk factor equations, 0.65 QALYs using contemporary risk factor equations, and 0.51 QALYs using last observation carried forward.

Discussion: Incorporating updated risk factor equations into diabetes simulation models could improve estimates of long-term health outcomes and costs. Improved risk factor management in recent decades is associated with a modest QALY gain.

New simulation model for evaluating cost-effectiveness of treatments for people with diabetes without previous cardiovascular disease

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Abstract

A Study of Cardiovascular Events iN Diabetes (ASCEND) recruited 15480 participants with diabetes without previous cardiovascular disease, and is one of the largest diabetes trials conducted to date. Participants were recruited between 2005 and 2011 and followed up till 2017 for an average of 7 years. Using the high quality longitudinal participant data available in ASCEND, we developed a new framework for modelling long-term health outcomes and costs for people with diabetes without previous cardiovascular disease.

New risk equations were estimated using the ASCEND data, and these were integrated into a patient-level stochastic simulation model which predicts the likelihood of occurrence of cardiovascular, bleeding, cancer, amputation, end-stage renal disease and death events over the lifetime of a patient given their baseline characteristics. The simulation model was externally validated in a cohort of 18250 participants identified to match the ASCEND eligibility criteria from the UK Biobank, a longitudinal prospective observational cohort. The simulation model performed well for key cardiovascular and cancer outcomes. Where discrepancies between model predictions and observed event rates in the UK Biobank were found, the reasons behind the discrepancies were identified and appropriate adjustments were made to the risk equations. Estimates of hospital costs and health-related quality of life (QoL) associated with the adverse events in the simulation model, derived from the ASCEND data, were incorporated into the simulation model to quantify lifetime cost and QoL. The newly developed and validated

framework reflects event rates, costs and QoL in contemporary diabetes cohorts. To demonstrate an application of the framework, we assess the cost-effectiveness of aspirin for primary prevention of cardiovascular disease in people with diabetes.

Development and Validation of a Microsimulation Model for Chronic Kidney Disease Progression in Type 2 Diabetes Patients in the United States: Michigan Model for Diabetes-Chronic Kidney Disease Model (MMD-CKD)

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Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are at higher risk for end-stage kidney disease (ESKD), cardiovascular disease (CVD) and mortality. Modeling CKD progression in these patients can help guide management to reduce the clinical and economic burdens of CKD.

We developed a discrete-state and discrete-time microsimulation model to predict changes in risk factors over time and simulate the progression of kidney disease and CVD in patients with T2D and CKD. Changes in risk factors for ESKD (urine albumin-to-creatinine ratio [UACR], estimated glomerular filtration rate [eGFR]), and risk equations for ESKD, myocardial infarction (MI), congestive heart failure (CHF), stroke, and death without dialysis or transplant were developed using individual-level longitudinal data for T2D populations and summary data from the published literature. We internally validated the model using Chronic Renal Insufficiency Cohort (CRIC) patients with T2D and CKD over 7-years and externally validated the model using the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial over 3-years.

This simulated event rates of ESKD, MI, CHF, stroke, and total mortality using estimated changes in key risk factors, and the related 95% confidence intervals included the observed event rates in both internal and external validation cohorts. The MMD-CKD model provided accurate estimates of disease progression among patients with T2D and CKD. Modeling disease progression in this population will allow assessment of the impact both screening and interventions for CKD, which may alter the health and economic burdens of CKD in T2D.

Mount Hood 2022 Challenges

Motivation:

The impact of model uncertainty on cost-effectiveness estimates of diabetes interventions is unknown. The aim of Mt Hood 2022 challenges is to examine the variation in cost-effectiveness estimates associated with two categories of diabetes interventions: a reduction in a patient's blood glucose levels and a reduction in weight. This variation will provide an estimate of model uncertainty, which will provide the basis for a publication. The challenge is broken into two components and they applicable to both type 2 and type 1 modelling groups.

Challenge 1: Revisiting the reference simulation

We will also ask groups to repeat the reference simulations for a standard patient that were in previous challenges and reported in the MT Hood model registry. This will enable model simulations to be compared across time and these values will be used to update the model registry: https://www.mthooddiabeteschallenge.com/registry. Previous reference simulations have often assumed that risk factors are held constant over time which is often unrealistic. Since the last Mt Hood challenge several risk factor time path equations have been published (eg https://onlinelibrary.wiley.com/doi/10.1111/dme.14656). Hence we ask all modelling groups to run the reference simulations under two scenarios: (i) risk factor values held constant (which was the assumption from the previous challenge); and (ii) allowing them to vary using equations or trajectories that are normally used in your simulation model. Treatment effects will assume to be a constant displacement from the usual time path.

Challenge 2: Simulating costs and cost-effectiveness

Following the 2018 Mt Hood Quality of life Challenge, the challenge employs average values or characteristics of patients enrolled in RCTs of common diabetes therapies. The average treatment effect of each category of intervention will be modelled by permanent reduction in HbA1c and body mass index. The results from this exercise will provide an indication of what factors influence the cost-effectiveness of these interventions. The challenge will also examine how the estimated incremental QALYs, incremental costs and ICERs vary for a cohort of patients with a history of myocardial infarction and following the inclusion of unrelated future medical costs.

Model Inputs:

Utility Values

The challenge uses the health utility values from the 2018 Mt Hood Quality of life Challenge for type 2 diabetes and newly added health utility values for type 1 diabetes (Table 1). It will be adequate to use point estimates and not model second order uncertainty if the model allows it.

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

For the challenge, please apply disutility values only to complication events described in the instructions as far as possible. If this is not possible and your model **requires** you to apply additional disutilities for certain health states (e.g. a raised BMI health state which is independent of BMI's effect on complication events) - please report these disutilities here. Please also keep baseline utilities constant across all ages as set out in instruction table 1. Where possible, please do not change baseline utilities by age. However, if your model requires you to do so – please report this in the Excel sheet.

Note: please make sure to avoid confusion with utility/disutility terminology in loading the models and in reporting results. The "Utility/Disutility Values" column in Table 1 reports "utility" only for diabetes without complication (which is positive). The remaining items (all negative) are disutility and are incremental.

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

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

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

Table 1. Utility values by categories of diseases/complications

Disease category	Complication level provided in Mt. Hood QoL challenge	Type 2 diabetes [a]			Type 1 diabetes *		
		Utility/Disutility Values	Lower 95% CI	Upper 95% CI	Utility/Disutility Values	Lower 95% CI	Upper 95% CI
Baseline utility value	Diabetes without complications	0.785	0.681	0.889	0.900[b]	0.880[b]	0.930[b]
Acute metabolic disorder	Minor hypoglycemia event	-0.014	-0.004	-0.004			
	Major hypoglycemia event	-0.047	-0.012	-0.012	-0.002[c]	-0.004[c]	-0.000[c]
	Major hyperglycemic event				−0.071[d]	-0.116[d]	-0.026[d]
Comorbidity	Excess BMI (each unit above 25 kg/m^2)	-0.006	-0.008	-0.004	-0.005[c]	-0.009[c]	-0.001[c]
Retinopathy	Cataract	-0.016	-0.031	-0.001			
	Moderate non-proliferative background diabetic retinopathy	-0.040	-0.066	-0.014	-0.027[c]	-0.048[c]	-0.005[c]
	Moderate macular edema	-0.040	-0.066	-0.014			
	Vision-threatening diabetic retinopathy	-0.070	-0.099	-0.041			
	Severe vision loss	-0.074	-0.124	-0.025			
Nephropathy	Proteinuria	-0.048	-0.091	-0.005			
	Renal transplant[1]	-0.082	-0.137	-0.027	-0.053[e]	-0.077[e]	-0.029[e]
	Hemodialysis	-0.164	-0.274	-0.054	-0.082[e]	-0.128[e]	-0.036[e]
	Peritoneal dialysis	-0.204	-0.342	-0.066			
Neuropathy	Peripheral vascular disease	-0.061	-0.090	-0.032			
	Neuropathy	-0.084	-0.111	-0.057	-0.236[c]	-0.299[c]	-0.173[c]
	Active ulcer	-0.170	-0.207	-0.133	-0.125[c]	-0.226[c]	-0.023[c]
	Amputation event	-0.280	-0.389	-0.170	-0.117[c]	-0.225[c]	-0.009[c]
Cerebrovascular disease	Stroke	-0.164	-0.222	-0.105	−0.291[b]	−0.475[b]	−0.108[b]
Coronary heart disease	Myocardial infarction	-0.055	-0.067	-0.042			
	Ischemic heart disease	-0.090	-0.126	-0.054	−0.181[b]	−0.331[b]	−0.031[b]
	Heart failure	-0.108	-0.169	-0.048	-0.058[f]	-0.101[f]	-0.015[f]
	Percutaneous revascularization				+0.025[c]	-0.051[c]	0.101[c]
	Coronary revascularization				-0.0787[c]	-0.218[c]	0.060[c]

Source: [a] Beaudet et al. 2014 [1]; [b] Solli et al 2010 based on EQ-5D-3L [2]; [c] Peasgood et al 2016 based on EQ-5D-3L [3]; [d] Hart et al 2003 based on EQ-5D-3L [4]; [e] Ahola et al 2010 based on 15D; [f] Coffey et al 2002 based on QWB-SA [5]; Abbreviations: QoL, quality of life; CI, confidence interval; T2DM, type 2 diabetes; BMI, body mass index. [1]The utility decrement and its 95% confidence interval for renal transplant was assumed to be the half of those for haemodialysis.* Compiled by An Tran-Duy (an.tran@unimelb.edu.au) on behalf of the COSMO-T1D modelling group. Note that the 95% CIs were not reported in Hart et al (source: d) and Ahola et al (source: e) and were reconstructed based on t-value, p-value, sample size and/or standard error where relevant.

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 2. Any other baseline patient characteristics that your model may require can be sourced from publicly available literature (but please document this including sources in "Baseline Characteristics" tab in the accompanying Excel spreadsheet).

Table 2: Patient Baseline Characteristics

Patient Characteristics	Type 2 diabetes [a]		Type 1 diabetes [b]	
	Men	Women	Men	Women
Current age	66	66	37	37
Duration of diabetes	8	8	22	22
Current/former smoker	N	N	N	N
Ethnicity	White	White	White	White
HbA1c. %	7.5	7.5	8.1	8.1
Systolic Blood Pressure, mmHg	145	145	127	127
Diastolic Blood Pressure, mmHg	80	80	73	73
Total Cholesterol, mmol/l	5.2	5.2	4.8	4.8
HDL Cholesterol, mmol/l	1.3	1.3	1.6	1.6
LDL Cholesterol, mmol/l	3.0	3.0	2.7	2.7
Triglycerides, mmol/L	2.0	2.0	1.2	1.2
BMI	28	28	25	25
Albumin: creatinine ratio	14.2	14.2		
PVD	N	N	N	N
Micro or macro albuminuria (albuminuria >50)	N	N	N	N
Atrial fibrillation	N	N	N	N
eGFR (ml/min/1.73 m2)	70	70	96	96
WBC (x10^9/l)	7	7		
Heart rate (bpm)	79	79		
Haemoglobin (g/dl)	14	14		
Prior history of macrovascular disease	N	N	N	N
Prior history of microvascular disease	N	N	N	N

Source: [a]ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline; see Appendix 1 for summary table; [b] Tran-Duy et al 2020 [6]

Costs

The perspective of the cost analysis is the health care system in the United Kingdom. Table 3 shows mean complication costs of diabetic patients obtained from UK literature. Please apply the same set of complication costs for both men and women and for both type 2 and type 1 diabetes individuals.

Please apply costs only to complication events described in the instructions as far as possible. To give example, if your model usually incorporates increased costs from raised BMI increases independently of complication events which occur, please turn this off if possible. If not possible to model costs only for complication events, then please report any additional costs.

Additionally, please keep baseline costs in the absence of complications constant across all ages as set out in instruction table 3, apart from for step 7 of Challenge 2 – where costs of unrelated medical expenditure vary by age. If possible, please do not otherwise change baseline costs by age. However, if your model requires you to do so – please report this in the excel spreadsheet.

Table 3 Complication costs (£, 2017-18 prices)

	Fatal cost	Non-fatal cost	Cost in subsequent years	Source
Ischemic heart disease/Angina	6,070	14,001	3,550	Alva et al. 2015 [7]
Myocardial infarction	3,318	9,518	3,424	Alva et al. 2015 [7]
Heart failure	2,825	5,650	4,277	Alva et al. 2015 [7]
Coronary revascularisation	-	8,302	3,550	Keng et al. 2021 [8] & Alva 2015 [7]
Stroke	6,463	10,755	3,534	Alva et al. 2015 [7]
Amputation	9,825	15,153	5,328	Alva et al. 2015 [7]
Blindness	0	4,247	2,206	Alva et al. 2015 [7]
Haemodialysis	0	43,359	43,359	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Renal failure / transplant	10,289	20,578	20,578	NHS Blood and Transplant 2009 [11]
Ulcer	0	7,076	1,072	Kerr et al. 2014 [12]
Peripheral vascular disease	0	4,698	1,010	Baxter et al. 2016 as cited in Ramos et al. 2019
Cataract operation	0	2,636	178	Davies et al. 2012 [9], 2016 [13] as cited in Ramos et al. 2019 [10]
Neuropathy	0	29	29	Davies et al. [13] as cited in Ramos et al. 2019 [10]

Gangrene treatment	0	3,694	0	Davies et al. [13] as cited in Ramos et al. 2019 [10]
Retinopathy laser treatment	0	1,176	0	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Peritoneal Dialysis	0	32,556	32,556	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Severe hypoglycaemia (req. med. assistance)	0	1,470	0	Evans et al. 2017 [14] as cited in Ramos et al. 2019 [10]
Severe hypoglycaemia (req. non med. assistance)	0	433	0	Evans et al. 2017 [14] as cited in Ramos et al. 2019 [10]
Non-severe hypoglycaemia	0	4	0	Evans et al. 2014 [15] as cited in Ramos et al. 2019 [10]
Cost in the absence of complications	1,990			Alva et al. 2015 [7]

Table 4 Mean Intervention effect costs (£, 2017-18 prices) (assume applied every year while patients are alive in the simulation)

Intervention	Mean effect	Mean annual cost (£)
Blood glucose intervention 1:	0.5% point reduction in HbA1c & no effect on BMI	12
Blood glucose intervention 2:	0.9% point reduction in HbA1c &) 1-unit **increase** in BMI (kg/m2) increase in BMI	320
Blood glucose intervention 3:	1.5% point reduction in HbA1c & 1-unit **reduction** in BMI	3810

Challenge simulation

Step 1: Run a simulation using the baseline risk factors from Table 2 held constant over a 40-year period for type 2 diabetes and a 70-year period for type 1 diabetes, separately for males and for females

This simulation should match both the 2018 Mt Hood challenge and the reference case simulations which are on the Mt Hood website: (https://www.mthooddiabeteschallenge.com/refsim). Ensure the costs and health outcomes are **not discounted** for this challenge.

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

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

Step 2: Reference simulation of common treatment effects

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

(i) 0.5%-point reduction in HbA1c;
(ii) 10mm Hg reduction in Systolic Blood Pressure;
(iii) 0.5 mmol/l (19.33 mg/dl) reduction in LDL Cholesterol
(iv) 1-unit reduction in BMI (kg/m2)
(v) All 4 of the interventions above applied simultaneously#

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

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

Using the "Utility/disutility" values in Table 1 run the baseline simulation and estimate expected QALYs, assuming that decrements apply to the year of the of the event and are similarly applied to each subsequent year. However, if temporary events/states such as hypoglycaemia are modelled, it is likely that these decrements only apply to the year of the event. If so, please document this.

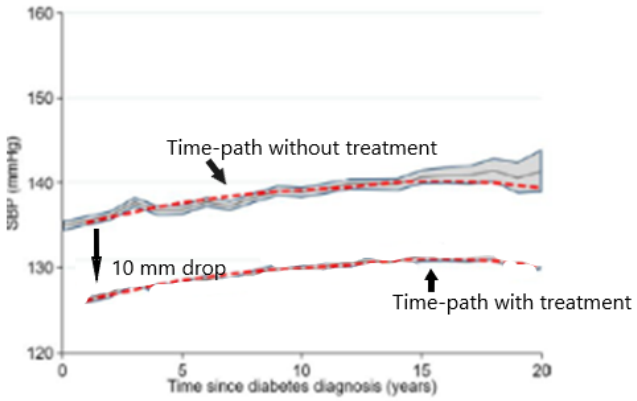
Run each of the four interventions listed in Step 2 to estimate the expected QALYs and calculate the incremental QALYs compared to the baseline (control). Extract the results and add to the accompanying Excel workbook (in tab labelled "Time paths & Outcomes").

Be sure to report incremental QALYs so that a negative value indicates worse QALYs (not inverting to account for a positive value indicating more disutility)

Step 4: Reference simulation of common treatment effects when risk-factor time-paths are NOT held constant

The simulation in step 1 does not capture the drift that can occur in many risk factors over time eg. the gradual increase in HbA1c. To understand what impact change in risk factors may have on incremental benefits the second component of this challenge is to redo the four simulations outlined in step 2 using the actual risk factor time paths or assumptions regularly used in your model. Please assume that treatment effects are permanent vertical displacements from the trajectories without intervention time-paths.

As an example consider the blood pressure treatment simulation – the treatment will permanently reduce SBP 10 mm Hg below the projected trajectory of SPB without treatment. Similarly, please allow all risk factors that are normally projected in your model to vary. So, when simulating the blood pressure lowering intervention allow HbA1c, LDL, BMI and other risk factors to follow the time-path predicted by your model without any treatment effect.



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

Challenge 2: Simulating costs and cost-effectiveness of hypothetical interventions

Challenge two involves a cost-effectiveness evaluation on a hypothetical cohort of the male and female patients that have been simulated in the first challenge. For this challenge assume that there are equal numbers of females & males. Groups are asked to report overall cost-effectiveness results for the cohort in the remaining challenges.

Step 5: Simulate three glucose lowering interventions

Re-run the simulation with three hypothetical interventions affecting blood glucose and BMI that capture initial and permanent reductions in common risk factors from time paths modelled in Step 1. Table 4 presents the effects of the interventions and respective annual costs.

It is important in each simulation that all risk factors are kept constant between simulations and limit variation to the intervention effects and costs as per instructions in the steps below. This includes assumptions around biomarker evolution; i.e. HbA1c and BMI should be kept constant over time and not allowed to change over time (i.e., drift).

Please apply the same effect and annual costs for both men and women over the whole simulation period. These costs are unchanged by the occurrence of complications. Assume that the interventions will not have an effect on any other risk factors than HbA1c and BMI. Finally, assume adherence to each intervention to be 100% during the whole simulation period. Although the interventions are hypothetical, their effect size is based on a recent meta-analysis of glycaemic drugs [https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1307] and their costs on the British National Formulary (BNF).

To estimate QALYs, use the utility values from Table 1 and follow the same assumptions as in Step 3. Estimate non-intervention costs (complications and management) by applying the costs from Table 3. Document any additional health states and/or costs used beyond those in Table 3.

The main outputs required are:

- incremental QALYs,
- incremental costs and
- incremental cost-effectiveness ratios

Report the above for the overall cohort of 50:50 males/females Conduct these simulations from a UK perspective, using and reporting costs in UK currency (£) and **setting the discount rate to 3.5%** for QALYs and costs prior to running the simulations.

Please use the minimum number of loops to reach convergence for the main outputs of interest. Report the number of loops used in each simulation.

Extract the results and add to the accompanying Excel workbook (in tab labelled "costs & ICERs"). Do not forget to include traces (numerical or curves) for input values of HbA1c and BMI risk factors.

Be sure to report incremental QALYs and costs of each intervention relative to no intervention so that a negative value indicates worse QALYs for the intervention compared to no intervention (not inverting to account for a positive value indicating more disutility)

Step 6: Estimate incremental QALYs and incremental costs for patients with a history of myocardial infarction (optional)

Re-run the simulation for a cohort of patients with a history of prior myocardial infarction again using the mean intervention costs provided in Table 4. If your model requires a number of years since the event, please use 5 years for all patients. Re-run for each of the blood glucose interventions, estimate the expected incremental QALYs and incremental costs, and calculate ICERs for each intervention compared to no intervention. Extract the results and add to the accompanying Excel workbook (in tabs labelled "Costs & ICERs").

Step 7: Estimate the ICERs for each intervention including estimates of future unrelated medical costs (optional)

Re-run Step 5 with the addition of unrelated medical costs (Table 5). These can be added to your model as annual costs unrelated to complications. These costs are assumed to remain unchanged by the occurrence of complications. Table shows separate costs by age group and sex, these should be included where possible. If this is not possible, collapse to mean values where required and make a note of this.

Table 5 Total annual expenditure on unrelated medical cost (£, 2017-18 prices)

	Men	Women
Aged 65-69	1,737	1,659
Aged 70-74	2,085	1,989
Aged 75-79	2,742	2,565
Aged 80-84	3,189	2,962
Aged 85+	3,694	3,339

Source: Briggs et al 2018 [16]

Extract incremental QALYs and incremental costs, and calculate ICERs for each intervention compared to no intervention and add to the accompanying Excel workbook (in tab labelled "Costs & ICERs"). **Again please report overall results for the cohort (which will be the results that will be focused on in the challenge).** Groups can also report subgroups if they wish to further explain their results.

Summary of findings:

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

A) Based on your results in Step 5, which intervention(s) were costs-effective at a £20,000 per QALY threshold?
B) Based on your results in Step 7, report which intervention(s) were costs-effective at a £20,000 per QALY threshold?
C) Provide an overview of what you learnt from this challenge.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MH MALMO CHALLENGE – ICER challenge_GROUP") to Mount Hood at: mthood2020@gmail.com by **12 September 2022.** Please replace GROUP with your modelling group name before submission.

APPENDIX 1

ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline

https://doi.org/10.1111/j.1464-5491.2005.01596.x

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

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

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

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Models Participating in 2022 Challenges

- **ASCEND (Type 2 Diabetes)**
- **Cardiff Model (Type 1 & Type 2 Diabetes)**
- **CHIME (Type 2 Diabetes)**
- **COSMO (Type 1 Diabetes)**
- **DOMUS (Type 2 Diabetes)**
- **ECHO-T1DM (Type 1 Diabetes)**
- **ECHO-T2DM (Type 2 Diabetes)**
- **IHE-DCM (Type 2 Diabetes)**
- **IQVIA Core Diabetes Model (Type 1 & Type 2 Diabetes)**
- **MDM Treatment Transitions Model (TTM) (Type 2 Diabetes)**
- **MICADO Model (Type 2 Diabetes)**
- **PRIME (Type 2 Diabetes)**
- **UKPDS Outcomes Model (Type 2 Diabetes)**

ASCEND Model

Contact details of main developer:

Mi Jun Keng, Health Economics Research Centre – University of Oxford
[mijun.keng@ndph.ox.ac.uk]

Type of diabetes: Type 2 Diabetes

Brief Description:

A Study of Cardiovascular Events iN Diabetes (ASCEND) recruited 15480 participants with diabetes without previous cardiovascular disease, and is one of the largest diabetes trials conducted to date. Participants were recruited between 2005 and 2011 and followed up till 2017 for an average of 7 years. Risk equations were estimated using the ASCEND data, and these were integrated into a patient-level stochastic simulation model which predicts the likelihood of occurrence of cardiovascular, bleeding, cancer, amputation, end-stage renal disease and death events over the lifetime of a patient given their baseline characteristics. The simulation model was externally validated in a cohort of 18250 participants identified to match the ASCEND eligibility criteria from the UK Biobank, a longitudinal prospective observational cohort. The simulation model performed well for key cardiovascular and cancer outcomes. Where discrepancies between model predictions and observed event rates in the UK Biobank were found, the reasons behind the discrepancies were identified and appropriate adjustments were made to the risk equations.

Estimates of hospital costs and health-related quality of life (QoL) associated with the adverse events in the simulation model, derived from the ASCEND data, were incorporated into the simulation model to quantify lifetime cost and QoL. The newly developed and validated framework reflects event rates, costs and QoL in contemporary diabetes cohorts, and can be used to model long-term health outcomes and costs for people with diabetes without previous cardiovascular disease.

Funding source for development of model: The development of the model was supported by a grant from the British Heart Foundation Centre of Research Excellence, Oxford (grant code: RE/13/1/30181).

Key Publications:

- Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, on behalf of the ASCEND Study Collaborative Group. Hospital Costs Associated with Adverse Events in People with Diabetes in the UK. Diabetes, Obesity and Metabolism 2022;1-10. doi: 10.1111/dom.14796

- Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, on behalf of the ASCEND Study Collaborative Group. Decrements in Health-Related Quality of Life Associated with Adverse Events in People with Diabetes. Diabetes, Obesity and Metabolism 2022;24:530–8. doi: 10.1111/dom.14610

Cardiff Model

Contact details of main developer:

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

Type of diabetes: Type 1/2 Diabetes

Brief Description:

The Cardiff Model is a fixed-time increment stochastic simulation model programmed in C++ and Visual Basic for Applications. It is designed to evaluate the impact of therapeutic intervention in Type 1 and Type 2 diabetes. The Type 1 Diabetes Model utilises data from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study (microvascular complications) and the Swedish National Diabetes Registry (cardiovascular complications). The Type 2 diabetes model fully implements UKPDS 68 and 82 risk equations and has recently been updated to included risk equations derived from the DECLARE-TIMI 58 cardiovascular outcomes trial.

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). The model has recently been updated to include the kidney and cardiovascular protective effects reported in recent outcomes trials, and to also reflect contemporary guidelines for the management of diabetes.

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 84 and utilities from UKPDS 62, and supplemented with Type 1-specific data where published. The relationship between both weight change and the frequency and severity of hypoglycaemia on costs and quality of life is also captured.

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

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

Key Publications:

- McEwan P, Morgan AR, Boyce R, Bergenheim K, Gause-Nilsson IAM, Bhatt DL, Leiter LA, Johansson PA, Mosenzon O, Cahn A, Wilding JPH. The cost-effectiveness of dapagliflozin in treating high-risk patients with type 2 diabetes mellitus: An economic evaluation using data from the DECLARE-TIMI 58 trial. Diabetes Obes Metab. 2021;23(4):1020-1029
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CHIME Model

Contact details of main developer:

Jianchao Quan, School of Public Health, LKS Faculty of Medicine, University of Hong Kong [jquan@hku.hk]

Type of diabetes: Type 2 Diabetes

Brief Description:

The CHIME model is an individual-level discrete-time simulation model programmed in R. It integrates prediabetes and type 2 diabetes into a comprehensive model, particularly suitable for Chinese and East Asian populations. CHIME uses an integrated system of parametric equations that predict the annual probability of 13 outcomes: all-cause mortality, diabetes-related macrovascular events (myocardial infarction, ischemic heart disease, heart failure, and cerebrovascular disease), microvascular events (peripheral vascular disease, neuropathy, amputation, ulcer of the skin, renal failure, cataracts, and retinopathy), and development of diabetes status (for prediabetes). The simulation model recordes outputs including time to death and complications, annual incidence of complications and death, and changes in risk factors. Predictions are based on patient demographics, duration of diabetes, biomarker values, smoking status, and history of complications. CHIME was developed from a population-based cohort of individuals with prediabetes or type 2 diabetes in Hong Kong Clinical Management System (97,628 participants) from 2006 to 2017; and externally validated against the CHARLS cohort and nine simulated diabetes trials. The CHIME model can be used by health service planners and policymakers to evaluation population-level strategies on outcomes through their impact on risk factor levels.

Funding source for development of model: Research Grants Council (Hong Kong SAR)

Key Publications:

- Quan J, Ng CS, Kwok HHY, Zhang A, Yuen YH, Choi CH, Siu SC, Tang SY, Wat NM, Woo J, Eggleston K, Leung GM. Development and validation of the CHIME simulation model to assess lifetime health outcomes of prediabetes and type 2 diabetes in Chinese populations: A modelling study. PLOS Med 2021;18(6): e1003692.

COSMO-T1D Model

Contact details of main developer:

An Duy Tran, Melbourne School of Population and Global Health, University of Melbourne [an.tran@unimelb.edu.au]

Type of diabetes: Type 1 Diabetes

Brief Description:

The COSMO-T1D is a patient-level, probabilistic discrete-time simulation model based on an integrated system of 30 equations for predicting occurrence of diabetes-related complications and progression of risk factors for the complications. Data from the Swedish National Diabetes Register (NDR) were used for model development. The COSMO-T1D consists of 14 parametric proportional hazards models, of which 10 are used to predict probabilities of first and second acute complications (coronary vascular event, stroke, amputation, severe hypoglycaemia and severe hyperglycaemia), three to predict the probability of diagnosis of three chronic conditions (heart failure, peripheral vascular disease and end-stage renal disease), and one to predict the probability of all-cause mortality. Monte-Carlo methods are used to predict occurrence of the events within a year based on the estimated annual probabilities. When a coronary vascular event occurs, a multinomial logit model is used to predict if the event is myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Predictors of the risk equations include time-independent factors (e.g., age at disease onset, sex), time-varying risk factors (e.g., HbA1c, HDL cholesterol, eGFR) and time-varying history of complications (e.g., indicator for occurrence of stroke).

The COSMO-T1D uses seven linear regression models to predict progression of continuous risk factors (Hb1Ac, eGFR, BMI, HDL cholesterol, LDL cholesterol, triglycerides and systolic BP) and eight logistic regression models to predict changes in binary risk factors (smoking initiation, smoking cessation, development of microalbuminuria from non-albuminuria, macroalbuminuria becoming microalbuminuria, remission of microalbuminuria, development of macroalbuminuria from non-albuminuria, microalbuminuria becoming macroalbuminuria and remission of macroalbuminuria). Inputs of the model are individuals with pre-defined baseline characteristics (e.g., current age, age at disease onset, HbA1c, history of severe hypoglycaemia, time since last severe hypoglycaemia). Outputs of the model is a longitudinal dataset containing annual values of risk factors and indicators for occurrence of complications and death for each individual. COSMO-T1D allows minimization of first-order uncertainty by implementing Monte Carlo simulation with a large number of replications for each individual. Evaluation of an interventions for type 1 diabetes can be conducted by adapting the equations for risk factor progression and/or event risks to simulate its impact on changes in risk factor values and incidence of the complications. For a cost-utility analysis, decrements of health

utility and costs associated with the complications can be applied to the model output to estimate quality-adjusted life years and total healthcare costs.

Funding source for development of model: This study was supported by the National Health and Medical Research Council (NHMRC; grant number 1028335), the Australian Research Council's Discovery Early Career Researcher Awards scheme (DECRA; grant number DE150100309), and the Australian Research Council's Centre of Excellence in Population Ageing Research (CEPAR; grant number CE170100005). The Swedish Association of Local Authorities and Regions funds the Swedish National Diabetes Register (NDR) which was used as a data source for model development.

Key Publications:

- Tran-Duy A, Knight J, Palmer A, et al. (2020) A patient-level model to estimate lifetime health outcomes of patients with type 1 diabetes. Diabetes Care 43: 1741-1749
- Tran-Duy A, Knight J, Clarke P, Svensson AM, Eliasson B, Palmer A (2021) Development of a life expectancy table for individuals with type 1 diabetes. Diabetologia 64: 2228-2236. 10.1007/s00125-021-05503-6

DOMUS Model

Contact details of main developer:

Aaron Winn, MCW Pharmacy School, Medical College of Wisconsin, [awinn@mcw.edu]

Type of diabetes: Type 2 Diabetes

Brief Description:

The diabetes outcomes model for the US (DOMUS) is a microsimulation model that was developed using a multi-ethnic, real-world-data cohort of newly diagnosed Type II diabetics. The model was developed using the Kaiser Permanente Northern California (KPNC) Diabetes Registry, which is a well-described epidemiologic cohort with up to 13 years of follow-up from EMR and claims. We were able to identify over 130,000 newly diagnosed diabetes patients between 2005-2016 with up to 13-year follow-up. The DOMUS model integrates separate, but interdependent risk equations to predict events for each of the micro and macro-vascular events, hypoglycemia, dementia, depression, and death, and predictive models for eight biomarker levels. Model accounted for static demographic factors (e.g., race), neighborhood deprivation, smoking and dynamic factors, such as age, duration of diabetes, fifteen-possible glucose –lowering treatment combinations, biomarker levels, and history of diabetes-related events. Moreover, the models explicitly allow for a legacy effect (average A1c in the first year after diagnosis) for all outcomes. Extensive validation was done on a hold-out sample and model predictions in the validation sample closely aligned with the observed longitudinal trajectory of biomarkers and outcomes. Moreover, we examine the model performance within by age, race/ethnicity, and sex and found excellent predictive performance within subgroups.

Funding source for development of model: Predicting Future Health Disparities for U.S. Adults with Diabetes: Development and Application of the Multi-Ethnic U.S. Diabetes Outcomes Model (NIMHD R01 MD013420)

Key Publications:

N/A

ECHO-T1DM Model

Contact details of main developer:

Michael Willis, Swedish Institute for Health Economics [michael.willis@ihe.se]

Type of diabetes: Type 1 Diabetes

Brief Description:

The Economic and Health Outcomes Model of T1DM (ECHO-T1DM) is a stochastic, micro-simulation (patient-level) model, suitable for estimating long-term cost-effectiveness of the treatment of T1DM. The physiology of T1DM is captured using Markov health states for micro- and macrovascular complications and death.

The cycle lengths of ECHO-T1DM are 1 year and the time horizons are user-definable. The model account explicitly for both first-order and second-order uncertainty and are programmed in R with an Excel interface

ECHO-T1DM generates a user-defined number of hypothetical patients at simulation start based on user-defined probability distributions of glycemic status age, sex, ethnicity, disease duration, biomarker, smoking status, and health complications. Patient characteristics are updated each cycle.

Chronic kidney disease (CKD), neuropathy, and retinopathy are modeled in parallel. Progression rates, adjusted for HbA1c, T2DM duration and other biomarkers in line with current clinical understanding, steer transition between the different health states. Macrovascular complications consist of ischemic heart disease (IHD), myocardial infarction (MI), stroke, and heart failure (HF). Multiple sets of macrovascular risk equations are supported: Swedish National Diabetes Registry, Epidemiology of Diabetes Interventions and Complications study, and Framingham Heart study. Mortality in ECHO-T1DM is governed by risk equations and life-tables. Macrovascular event mortality is obtained from the selected macrovascular risk equation, and mortality is a competing risk for all other events.

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

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

ECHO-T1DM reports outcomes including cumulative incidences and rates (RRRs) of each health outcome of health complications, AE rates (HRs), LYs and QALYs, inferred cause of death and sources of disutility, biomarker evolution curves, mean time to rescue treatment, and a host of cost and cost-effectiveness metrics.

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

Key Publications:

N/A

ECHO-T2DM

Contact details of main developer:

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

Type of diabetes: Type 2 Diabetes

Brief Description:

The Economic and Health Outcomes Model of T2DM (ECHO-T2DM) is a stochastic, micro-simulation (patient-level) model, suitable for estimating long-term cost-effectiveness of the treatment of T2DM. The physiology of T2DM is captured using Markov health states for micro- and macrovascular complications and death. The cycle length is 1 year and the time horizon is user-definable. ECHO-T2DM accounts explicitly for both first-order and second-order uncertainty and is programmed in R with an Excel interface.

ECHO-T2DM generates a user-defined number of hypothetical patients at simulation start based on user-defined probability distributions of age, sex, ethnicity, disease duration, biomarker values like HbA1c and systolic blood pressure (SBP), smoking status, and health complications.Patient characteristics are updated each cycle.

Chronic kidney disease (CKD), neuropathy, and retinopathy are modeled in parallel.Progression rates, adjusted for HbA1c, T2DM duration and other biomarkers in line with current clinical understanding, steer transition between the different health states.Macrovascular complications consist of ischemic heart disease (IHD), myocardial infarction (MI), stroke, and heart failure (HF).Four sets of macrovascular risk equations are supported:UKPDS68, UKPDS82, ADVANCE, and the Swedish National Diabetes Registry.ECHO-T2DM supports UKPDS68 and UKPDS82 mortality risk equations, and mortality is a competing risk for all other events.

Treatment comparisons consist of initial treatments (multiple comparisons are supported), treatment intensification sequences, HbA1c target values, and treatment algorithms for hypertension, dyslipidemia, and excess weight.Anti-hyperglycemic drug profiles include initial biomarker changes (HbA1c, SBP, BMI, cholesterol, eGFR, and heart rate) and subsequent rate of biomarker evolution (i.e., “drift”), AE rates (e.g., hypoglycemia), relative risks for complications, treatment compliance, and discontinuation rules related to poor HbA1c control, AEs, contraindications, and/or reaching user-defined maximum treatment duration.Simpler profiles are supported for treating hypertension, dyslipidemia, and excess weight.

Unit costs for treatments, AEs, micro- and macrovascular complications (event costs and annual follow-up costs), revascularization procedures, and depression can be assigned.Macrovascular costs vary by fatal or non-fatal.Indirect costs are

supported.Baseline utility and disutility decrements for specific patient characteristics and health complications can be assigned.

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

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

Key Publications:

- Willis M, Johansen P, Nilsson A, Asseburg C. Validation of the Economic and Health Outcomes Model of T2DM (ECHO-T2DM). PharmacoEconomics 2017;35:375-396. DOI: https://doi.org/10.1007/s40273-016-0471-3
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- Neslusan C, Teschemaker A, Willis M, Johansen P, Vo L. Cost-Effectiveness Analysis of Canagliflozin 300 mg Versus Dapagliflozin 10 mg Added to Metformin in Patients with Type 2 Diabetes in the United States. Diabetes Ther 2018; 9(2): 565-581. DOI: https://doi.org/10.1007/s13300-018-0371-y
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- Willis M, Asseburg C, Nilsson A, Neslusan C. Challenges and Opportunities Associated with Incorporating New Evidence of Drug-Mediated Cardioprotection in the Economic Modeling of Type 2 Diabetes: A Literature Review. Diabetes therapy 2019; [Epub ahead of print]. DOI: 10.1007/s13300-019-00681-4

IHE-DCM Model

Contact details of main developer:

Adam Fridhammar, IHE The Swedish Institute for Health Economics [adam.fridhammar@ihe.se]

Type of diabetes: Type 2 Diabetes

Brief Description:

The IHE-DCM was developed to estimate the cost effectiveness of treatment interventions for type 2 diabetes mellitus (T2DM) using the cohort (representative patient) approach.

The IHE-DCM uses Markov health states that capture important microvascular and macrovascular complications and premature mortality resulting from T2DM. The cycle length is 1 year, and the time horizon is user-definable (up to 40 years).
The model was constructed in Microsoft® Excel 2013 with the aid of the built-in Visual Basic for Applications (VBA) and requires no plugins or external programs to use. To ensure the flexibility necessary to model many different applications, the model contains many user-definable parameters, including baseline characteristics of the cohort, choice of risk equations, treatment algorithms, unit costs and quality-adjusted life year (QALY) weights. The baseline characteristics of the cohort are demographics (e.g. age and gender), biomarkers (e.g. glycated hemoglobin [A1C] and blood pressure) and pre-existing complications (e.g. microalbuminuria and stroke).

At the start of the simulation, a cohort of hypothetical patients is defined from user-defined baseline characteristics and cloned for study arm. Each cohort is assigned a unique treatment algorithm. The treatment algorithms allow for modification of doses and addition of new medications when the initial treatment regimen does not achieve adequate A1C control. Medication to control blood pressure, blood lipids and overweight may also be applied. Treatment effects are modeled as absolute changes applied at simulation start or, for treatment intensification, during the year when it occurs in combination with annual drifts for each treatment line. The evolution of biomarkers is simulated annually until the predefined time horizon is reached. Adverse events, including up to 3 levels of severity of hypoglycemia, are applied using an annual event rate. Development and progression of complications and mortality are simulated next to the evolution of biomarkers. Risk equations govern the progression of the cohort between different health states.

The macrovascular and microvascular health states were selected to capture the most important complications for T2DM. To make the cohort approach feasible, the sets of micro- and macrovascular health states were divided into 2 separate Markov sub-models.

The 120 microvascular health states express the possible combinations of eye disease, kidney disease and lower extremity amputation states. The 100 macrovascular health states combine stages of ischemic heart disease (IHD), myocardial infarction (MI), stroke and heart failure. The user can choose to form a set of 4 macrovascular risk prediction equations, including the United Kingdom Prospective Diabetes Study (UKPDS) 68, UKPDS 82, Swedish National Diabetes Registry (NDR) and Australian Freemantle Diabetes Study (FDS), which are applied individually to each macrovascular health state. The user can choose between 2 sets of mortality equations, either the UKPDS 68 or UKPDS 82.

Unit costs and QALY weights, matching current treatment, distribution of health states and adverse events are applied to the cohort in each cycle. Model outcomes include mean survival, expected life-years, QALYs and direct costs. The outcomes are combined to compute incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs), among other outcomes.

Funding source for development of model: Internal funding

Key Publications:

- Lundqvist A, Steen Carlsson K, et al. Validation of the IHE Cohort Model of type 2 diabetes and the impact of choice of macrovascular risk equations. PLoS One. 2014;9(10): e110235.
- Willis M, Fridhammar A, Gundgaard J, Nilsson A, Johansen P. Comparing the Cohort and Micro-Simulation Modeling Approaches in Cost-Effectiveness Modeling of Type 2 Diabetes Mellitus: A Case Study of the IHE Diabetes Cohort Model and the Economics and Health Outcomes Model of T2DM. PharmacoEconomics. 2020;38(9):953-69.

IQVIA Core Diabetes Model

Contact details of main developer:

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Type of diabetes: Type 1 & 2 Diabetes

Brief Description:

The IQVIA -Core-Diabetes-Model (formerly 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 as 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 and progression equations including equations from the UKPDS82 and 90 (aside 68), several east Asian risk equations, the Swedish-National-Diabetes-Register for type 1 and type 2, the ADVANCE-risk-engine, the Fremantle-study, EDIC, Pittsburg 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.

Funding source for development of model: IQVIA internal funding

Key Publications:

- Ehlers LH, Lamotte M, Ramos M, Sandgaard S, Holmgaard P, Kristensen MM, Ejskjaer N. The cost-effectiveness of subcutaneous semaglutide versus empagliflozin in type 2 diabetes uncontrolled on metformin alone in Denmark. Diabetes Therapy https://doi.org/10.1007/s13300-022-01221-3.

- Michelle Tew, Michael Willis, Christian Asseburg, Andreas Nilsson, An Tran-Duy, Mark Lamotte, Mafalda Ramos, Lei Si, Hui Shao, Lizheng Shi, Ping Zhang, Phil McEwan, Wen Ye, William H. Herman, Shihchen Kuo, Chunting Yang, Deanna Isaman, Wendelin Schramm, Fabian Sailer, Alan Brennan, Laura Heathcote, Daniel Pollard, Chloe Thomas, Harry J. Smolen, James Gahn, Rishi Patel, José Leal, Alastair Gray, Talitha Feenstra, Andrew J. Palmer, Philip Clarke. Exploring structural uncertainty and impact of health state utility values on lifetime outcomes in diabetes economic simulation models: Findings from the Ninth Mount Hood Diabetes Quality-of-Life Challenge. Accepted in Medical Decision Making 2021. 1-13https://doi.org/10.1177%2F0272989X211065479
- Jendle J, Eeg-Olofsson K, Svensson AM, Franzen S, Lamotte M, Levrat-Guillen F. Cost-Effectiveness of the FreeStyle Libre® system versus Blood Glucose Self-Monitoring in individuals with Type 2 Diabetes on Insulin Treatment in Sweden. Diabetes Therapy 2021 https://doi.org/10.1007/s13300-021-01172-1.
- Ehlers LH, Lamotte M, Ramos M, Sandgaard S, Holmgaard P, Frary EC, Ejskjaer N. The cost-effectiveness of oral semaglutide versus empagliflozin in type 2 diabetes in Denmark. Journal of Comparative Effectiveness Research 2021. DOI: 10.2217/cer-2021-0169
- McCrimmon RJ, Lamotte M, Ramos M, Alsaleh AJO, Souhami E, Lew E. Cost-Effectiveness of iGlarLixi Versus iDegLira in Type 2 Diabetes Mellitus Inadequately Controlled by GLP-1 Receptor Agonists and Oral Antihyperglycemic Therapy. Diabetes Therapy 2021 https://doi.org/10.1007/s13300-021-01156-1.
- Ramos M, Men P, Wang X, Ustyugova A, Lamotte M. Cost-effectiveness of empagliflozin in patients with type 2 diabetes and established cardiovascular disease in China. Cost Ef Resour Alloc (2021) 19:46 https://doi.org/10.1186/s12962-021-00299-z.
- Salem A, Hu H, Ramos M, Zhong H, Lamotte M. Potential clinical and economic impact of optimised maintenance therapy on discharged COPD patients after hospitalisation for an exacerbation in China. BMJ Open 2021;11:e043664. doi:10.1136/bmjopen-2020-043664.
- Ehlers LH, Lamotte M, Monteiro S, Sandgaard S, Holmgaard P, Frary EC, Ejskjaer N. The Cost-Effectiveness of Empagliflozin Versus Liraglutide Treatment in People with Type 2 Diabetes and Established Cardiovascular Disease. Diabetes Therapy https://doi.org/10.1007/s13300-021-01040-y
- Salem A, Men P, Ramos M, Zhang YJ, Ustyugova A, Lamotte M. Cost-Effectiveness Analysis of Empagliflozin Compared to Glimepiride In Patients with Type 2 Diabetes In China. Journal of Comparative Effectiveness Research 2021 https://doi.org/10.2217/cer-2020-0284.

MICADO Model

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Type of diabetes: Type 2 Diabetes

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.

Funding source for development of model: RIVM, Diabetes Foundation, Dutch Healthcare Institute

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 Diabetic Medicine Volume 32, Issue 12, pages 1580–1587, December 2015

MDM - Treatment Transition Model (TTM)

Contact details of main developer:

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Type of diabetes: Type 2 Diabetes

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.

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

Key Publications:

- 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.
- 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.

PRIME Model

Contact details of main developer:

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Type of diabetes: Type 2 Diabetes

Brief Description:

The PRIME Diabetes Model is a product-independent analysis tool designed to evaluate long-term clinical and cost outcomes for populations with type 1 (T1D) or type 2 diabetes mellitus (T2D). Following systematic literature reviews to identify longitudinal study data, existing models and risk formulae for T1D or T2D populations, the model was developed in line with good practice guidelines to simulate disease progression, diabetes-related complications (myocardial infarction, ischemic heart disease, stroke, heart failure, revascularization, renal failure, neuropathy, foot ulcer, amputation, macular edema and blindness), adverse events (including hypoglycemia) and mortality. The model runs as a patient-level simulation capable of simulating treatment algorithms, risk factor progression, and project the cumulative incidence of mortality, complications and adverse events to evaluate life expectancy, quality-adjusted life expectancy, direct and indirect costs, along with standard measures of cost-effectiveness. The model combines published risk equations (using a weighted model averaging approach for several complications) and Monte Carlo methods to evaluate the risk of mortality and diabetes-related complications based on simulated patient characteristics, risk factors and history of complications. Outcomes associated with novel treatment and management approaches can be modeled through their effects on conventional risk factors and/or by directly modifying the risk of diabetes-related complications. Validation analysis comparing outcomes predicted by the model with those from published studies has shown that the PRIME Diabetes Model can project long-term patient outcomes that are consistent with those reported for a number of long-term studies.

Funding source for development of model: Financial support for the development of the PRIME Diabetes Model was provided by Eli Lilly and Company, Indianapolis, USA.

Key Publications:

- Valentine WJ, Pollock RF, Saunders R, Bae J, Norrbacka K, Boye K. The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus. Value Health. 2017; 20(7): 985-91
- Pollock RF, Norrbacka K, Boye KS, Osumili B, Valentine WJ. The PRIME Type 2 Diabetes Model: a novel, patient-level model for estimating long-term clinical and

cost outcomes in patients with type 2 diabetes mellitus. J Med Econ. 2022; 25(1): 393-402

UKPDS Outcomes Model

Contact details of main developer:

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Type of diabetes: Type 2 Diabetes

Brief Description:

The UKPDS Outcomes Model (UKPDS-OM) is based on patient-level data from the United Kingdom Prospective Diabetes Study (UKPDS). It simulates type 2 diabetic populations modelling the occurrence of eight diabetes-related complications (MI, 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. The first version of the model was published in 2004 (known as UKPDS OM I) and an enhanced version that was based on up to 10 years of additional information from UKPDS study was published in 2013 (UKPDS OM2) as well as set of risk factor time path equations published in 2021 (doi.org/10.1111/dme.14656).

Elements of the UKPDS Outcomes Models have been widely used in many other diabetes simulation models.

Funding source for development of model: The UKPDS study received funding from the UK Medical Research Council, the British Diabetic Association, the UK Department of Health, the National Eye Institute and the National Institute of Diabetes

and Digestive and Kidney Disease (the US National Institutes of Health), the British Heart Foundation, The Wellcome Trust, the Charles Wolfson Charitable Trust, the Clothworkers' Foundation, the Health Promotion Research Trust, the Alan and Babette Sainsbury rust, the Oxford University Medical Research Fund Committee. Funding was also provided by pharmaceutical companies including Novo-Nordisk, Bayer, Bristol-Myers Squibb, Hoechst, Lilly, Lipha and Farmitalia Carlo Erba, GlaxoWellcome, SmithKline Beecham, Pfizer, Zeneca, Pharmacia and Upjohn, and Roche provided grants for health economics and epidemiological studies.

The development of the UKPDS OM 2 was supported by the following grants: Australian National Health and Medical Research Council project grant no. 512463 and capacity building grant no. 571372. and UK Medical Research Council project grant on disease modelling (grant ID: 87386).

Key Publications:

- Leal, J, Alva, M, Gregory, V, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med. 2021; 38:e14656. https://doi.org/10.1111/dme.14656
- 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.