Implementation of UKPDS 82 equations in the CDM

PRESENTED AT THE CDM USER FORUM IN DUBLIN, 3RD NOVEMBER 2013

Implementation of UKPDS 82 equations in the CDM

Outline

- Validation
  - The CDM was validated against published findings in Diabetologia (September 2013)[1]
    - Internal validation: CDM projections vs. published findings of UKPDS cohort profile projected over 25 years
    - Comparison using "old" vs. "new" equations: The CDM was compared to published findings for three age groups of the "Lipids in Diabetes Study" (LDS) cohort
- Implications inside cost effectiveness analysis (CEA)
  - The CDM was applied with "old" and "new" set of equations to assess the implications (trends) inside CEA.

1) Hayes et al. UKPDS Outcomes Model 2, Diabetologia (September 2013), Volume 56, Issue 9

UKPDS 82 (OM2) Equations. Validation - 1

Key Points

- Objective
  - To reproduce published Outcomes Model 2 (OM2)[1] findings to validate the implementation of new OM2 equations inside the CDM framework.
- Approach
  - We compared CDM projections against published findings
    1. CDM vs. internal validation of OM2 equations using UKPDS cohort profile projected over 25 years(Figure 2)[1]
    2. CDM vs. comparison of outcomes using OM1 vs. OM2 equations for three age groups of the "Lipids in Diabetes Study" (LDS) cohort (Table 2 and 3)[1]
- Findings
  - Internal Validation
    - Close reproduction of macro vascular endpoints, foot ulcer and mortality
    - Underestimation of ESRD, blindness and Amputation (reasons are the structural differences of related complication sub-models in CDM vs. OM)

1) Hayes et al. UKPDS Outcomes Model 2, Diabetologia (September 2013), Volume 56, Issue 9

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UKPDS 82 (OM2) Equations. Validation - 2

Key Points (continued)

- Findings (continued)
  - Comparison of OM1 vs. OM2 (using LDS cohort)
    - 10 Year LDS projections for three age groups (CDM vs. Table 2[1])
      - OM2: Published vs. CDM projections compare well for all age groups
      - OM1: Lower complication incidence in CDM vs. published results for MI, stroke, IHD and death
        - Reason: Subsequent risk adjustments in CDM for CV concomitant medications (ACE/ARB, statins, aspirin), presence/absence of renal disease and HbA1c
    - Life expectancy in 3 LDS age groups (CDM vs. Table 3[1])
      - OM2: similar
      - OM1: higher in CDM (close to published predictions using OM2 equations)
- Conclusion
  - OM2
    - CDM performed well in reproducing CV outcomes and mortality generated with the new OM2 equations (for both, UKPDS and LDS cohort)
    - Underestimation of ESRD, blindness and AMP → IMS suggests removing OM2 equations (structural differences between models) and using existing renal module within CDM
  - OM1
    - CDM projections produce higher incidence for macro-vascular events and mortality (close to published OM2 findings)
    - Reason: Subsequent risk adjustments and WHO life table data used for non diabetes specific mortality

UKPDS 82 (OM2) Equations. Validation - 3

Background

- New set of equations based on 5,102 UKPDS patients followed over 20 years (including 10 year post trial monitoring)
- New equations are based on data from the longest follow up study of patients with T2DM, including both:
  - Clinical trial data
  - Observational data
- 89,760 patient years of data
  - Almost doubled number of events
  - Greater statistical power of a much larger dataset leading to:
    - Greater precision
    - Additional risk factors (significant)
      - eGFR
      - White blood cell count
      - Haemoglobin count
      - Heart rate
    - Additional linkages between complications

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UKPDS 82 (OM2) Equations. Validation - 4

Validation - Approach

- To reproduce published Outcomes Model 2 (OM2)[1] findings.
- Validations presented in OM2 paper:
  1. Internal validation
     - Against PLD for the 5,102 UKPDS participants
  2. Comparison of OM1 vs. OM2
     - PLD data from 3,984 LDS (Lipids in Diabetes Study) unique patients.
- Validations conduced with CDM
  - Reproduction of Figure 2 and Table 2 & 3:
    1. Internal validation: UKPDS cohort projected over 25 years (Figure 2)
    2. Comparison of OM1 vs. OM2 using 3 age groups of LDS cohort (52, 62 and 72 years):
       - 10 year incidence (Table 2)
       - Life Expectancy (Table 3)

1) Hayes et al. UKPDS Outcomes Model 2, Diabetologia (September 2013), Volume 56, Issue 9

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UKPDS 82 (OM2) Equations. Validation - 5

Validation – Overall findings (preview)

- **Internal Validation** (UKPDS cohort over 25 years)
  - Close reproduction of
    - Macro vascular endpoints (CHF and stroke slightly lower in CDM)
    - Foot ulcer
    - Mortality
  - Strong underestimation of
    - ESRD
    - Blindness
    - Amputation

Reason → CDM model structure is different

- **OM2**: Patients at risk at simulation start
- **CDM**: Patients at risk if ancestor complication developed

- **Comparison of OM1 vs. OM2** (LDS cohort)
  - 10 Year LDS projections for three age groups
    - OM2: Published vs. CDM projections compare well for all age groups
    - OM1: CDM projections generated lower complication incidence vs. published results in MI, stroke, IHD and death
    - Reversed trend for MI and IHD (CDM produced higher risk scores in OM2)
  - Life expectancy in 3 LDS age groups: **similar**

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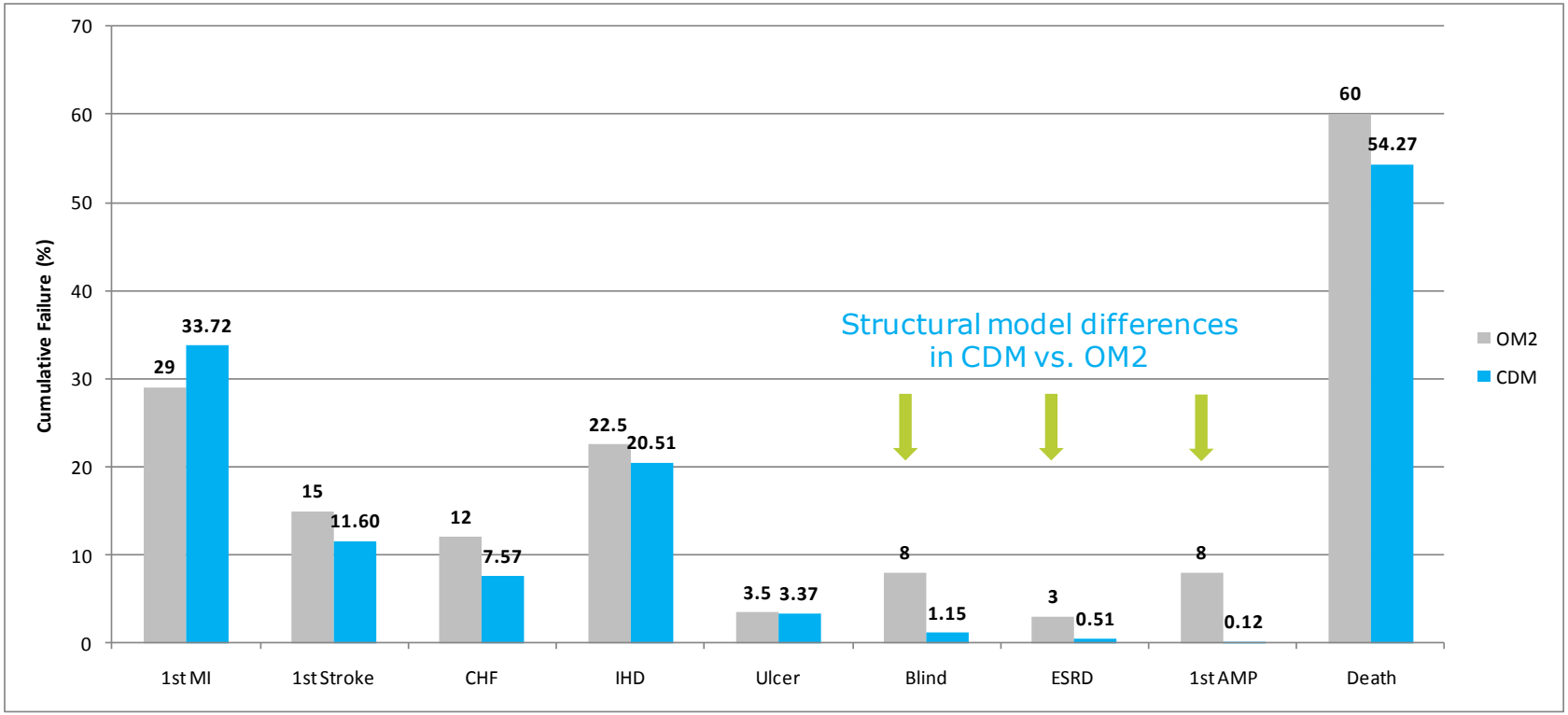
UKPDS 82 (OM2) Equations. Validation - 6

Validation of CDM against Figure 2 – Internal Validation

- Cumulative failure of relevant endpoints over 25 years in the UKPDS cohort – published OM2 vs. CDM findings



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UKPDS 82 (OM2) Equations. Validation - 7

LDS cohort (3 age groups): 10 year incidence in CDM vs. published findings (Table 2)

- Outcome comparison of CDM vs. published results are presented in the **next slide**.
- Findings are complemented by a **symbol and colour scheme** to help illustrate outcome trend (CDM vs. published).

	CDM lower	CDM higher	equal
OM2 Published vs. CDM	2	2	=
OM1 Published vs. CDM	1	1	=

Trend towards lower risk scores in OM2 vs. OM1 equations was reversed in CDM

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UKPDS 82 (OM2) Equations. Validation - 8

10 year CV incidence & death of LDS patients (3 age groups) in OM1 vs. OM2

Table 2) Published vs. CDM

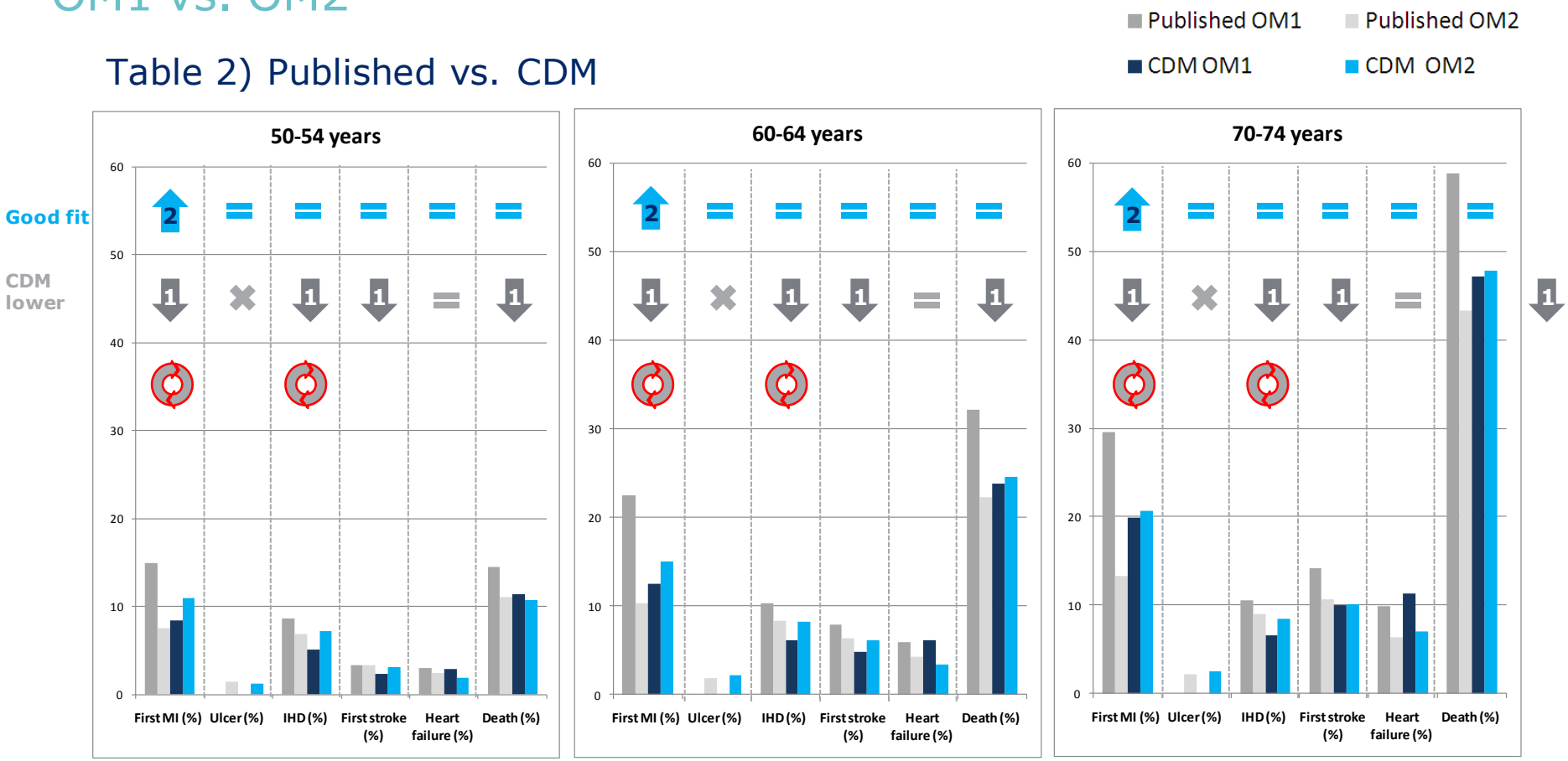

Table 2 - Hayes et al. UKPDS Outcomes Model 2, Diabetologia (September 2013), Volume 56, Issue 9

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UKPDS 82 (OM2) Equations. Validation - 9

Validation of CDM against Table 3

- Comparison of simulated life expectancy (95% CI) for three age groups from the LDS cohort – published vs. CDM results

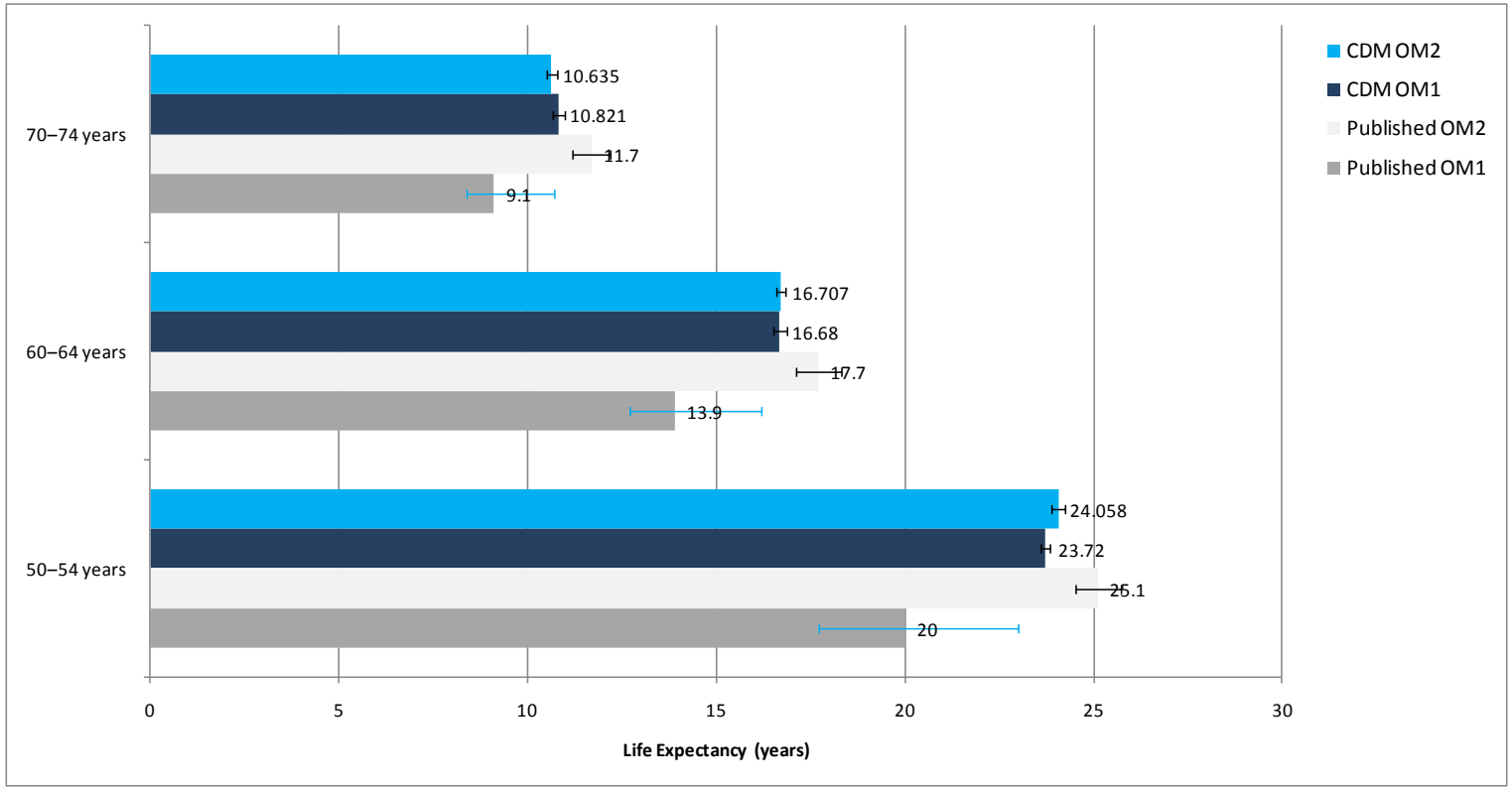

Table 3 - Hayes et al. UKPDS Outcomes Model 2, Diabetologia (September 2013), Volume 56, Issue 9

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UKPDS 82 (OM2) Equations. Validation - 10

Validation – Conclusion - 1

Published comparison of OM1 vs. OM2

- OM2 predicted fewer macro-vascular events and longer LE vs. OM1.
- Explanations:
  - OM2 equations are built upon a much larger dataset (**greater statistical power)**
  - OM1 projections represent **greater out of sample extrapolation**
  - Trend towards increased LE in OM2 is **consistent with downward secular trends in cardiovascular disease** and improvements in mortality.

UKPDS 82 (OM2) Equations. Validation - 11

Validation – Conclusion - 2

CDM reproduction

- OM2
  - CDM performed **well** in reproducing **CV outcomes** and **mortality** generated with the new OM2 equations (for both, UKPDS and LDS cohort)
  - Underestimation of ESRD, blindness and AMP: IMS suggests removing OM2 equations
- OM1
  - The trend towards higher macro-vascular event rates and mortality in OM1 vs. OM2 could not be reproduced by the CDM (OM1 predicted close to OM2)
  - This can be explained as the CDM applies a series of additional risk adjustments to the OM1 risk scores:
    - CV end points → Adjustments for aspirin, statins ACE/ARB, present renal disease and HbA1c
    - Non diabetes related mortality → WHO life tables

Implications of using OM2 vs. OM1 equations inside cost effectiveness analysis (CEA)

Implications of using UKPDS 82 equations in CEA - 1

Key Points – 1

- Objective
  - To assess implications (trends) of using the new OM2 equations in cost effectiveness analysis (CEA)
- Approach
  - Comparison of four hypothetical CEA scenarios using OM1 vs. OM2 equations
  - Treatments A to D (A: HbA1c -1%; B: SBP – 10 mmHG; C: BMI – 2Kg/m2; D: multifactorial (MF)) compared to no intervention (no effect at zero costs)
  - Annual treatment costs for products A, B and C were $US 500 and $1,500 for product
- Findings
  - OM2 equations translate in smaller incremental QALE for interventions lowering HbA1c and SBP but higher incremental QALE for BMI lowering (MF is balanced)
  - Negligible differences in incremental costs between OM1 and OM2
    - → larger ICER for interventions lowering HbA1c and SBP with OM2
    - → smaller ICER for BMI with OM2
    - → ICER for MF balanced (slightly higher) with OM2
  - 1% point HbA1c lowering translates into incremental QALE gain of 0.1 and 0.075 using OM1 vs. OM2, respectively

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Implications of using UKPDS 82 equations in CEA - 2

Key points - 2

- Conclusion
  - Overall we observed mixed results in the way risk factor changes translate into value (cost savings, QALE gain).
    - Reductions in HbA1c and SBP → less in incremental QALE gain.
    - Reduction in BMI → increased gain in incremental QALE
    - Increased LE with OM2 → more time for risk factor changes to translate into value
  - Reduced incremental QALE with OM2 likely due to systematic under prediction of foot ulcer, amputation and blindness when implemented in CDM
    - This trend will change once OM2 equations [for ulcer, amputation and blindness] are removed from the CDM
  - Overall no definitive consequence for cost effectiveness can be assessed when comparing OM2 versus OM1 within the CDM as it depends on a variety of input assumptions including cohort and treatment profile, selected morality approach (sub-model specific or "combined") etc.
  - However it is unlikely that using OM2 has the potential to change decision based CE thresholds.

Implications of using UKPDS 82 equations in CEA - 3

We explored implications of using OM2 vs. OM1 equations in two different case studies

Case study

- CEA 1) Product A reducing HbA1c by 1% points vs. no treatment
- CEA 2) Product B reducing SBP by 10 mmHg vs. no treatment
- CEA 3) Product C reducing BMI by 2 Kg/m2 vs. no treatment
- CEA 4) Multifactorial product D with effects of treatments A to D vs. no treatment
- Annual treatment costs for products A, B and C were $US 500 and $1,500 for product D

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Implications of using UKPDS 82 equations in CEA - 4

Case Study – Assumptions

- Cohort: UKPDS
- Time horizon: 50 years
- Discounting: 3%
- Treatments
  - CEA 1) Product A: HbA1c - 1% points vs. no treatment
  - CEA 2) Product B: SBP - 10 mmHg vs. no treatment
  - CEA 3) Product C: BMI - 2 Kg/m2 vs. no treatment
  - CEA 4) Multifactorial product D: effects A, B and C vs. no treatment
- Annual treatment costs
  - Products A, B and C: $US 500
  - Product D: $1,500
  - No treatment. $0
- Rescue therapy
  - None

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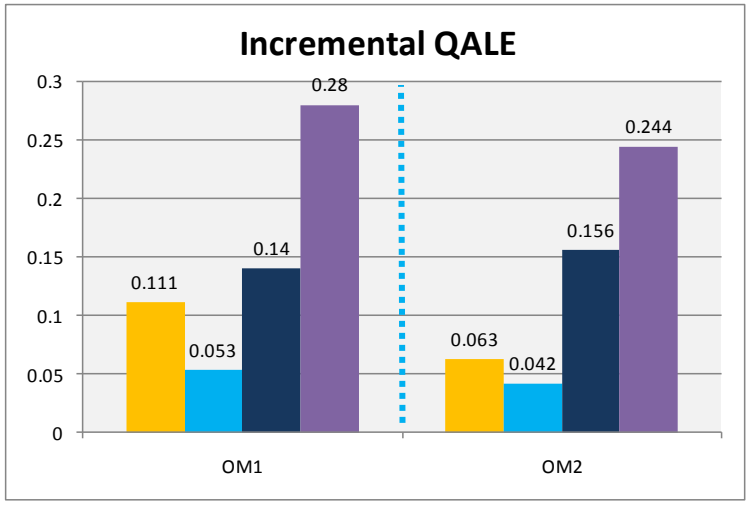
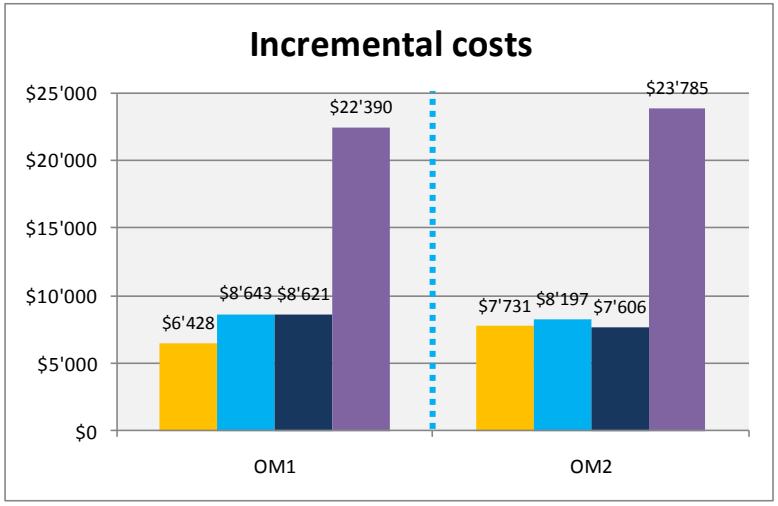
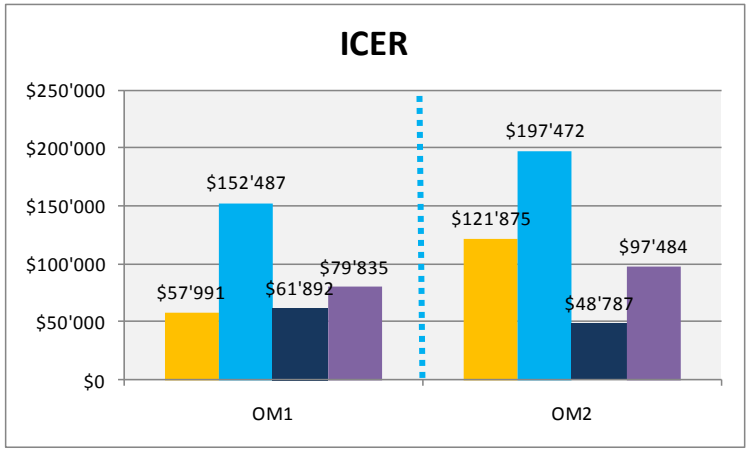
Implications of using UKPDS 82 equations in CEA - 5

Case Study 1 – Incremental outcomes







Differences in OM2 vs. OM1

- Smaller effect on incremental QALE for HbA1c and SBP change in OM2
- Larger BMI effect on incremental QALE in OM2
- Multifactorial treatment produced slightly lower incremental QALE
- Negligible changes for incremental costs between OM1 and OM2
- → larger ICER for HbA1c and SBP change in OM2
- → smaller ICER for BMI in OM2
- → Multifactorial ICER comparable

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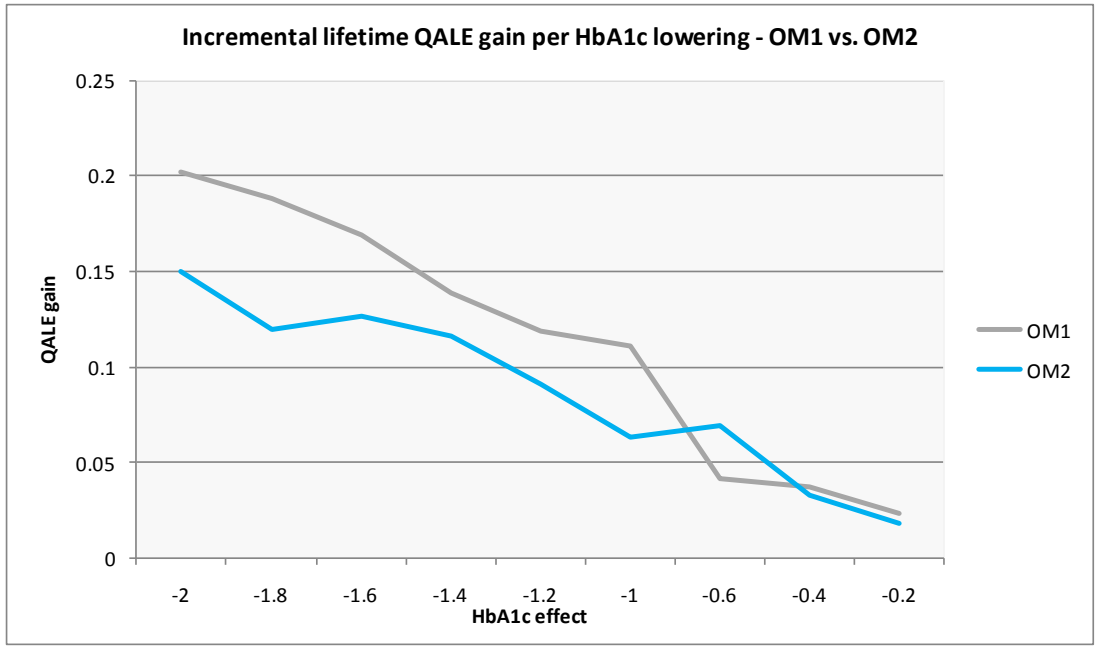
Implications of using UKPDS 82 equations in CEA - 6

Case Study 1 – Focus on relationship between HbA1c and QALE in OM1 vs. OM2

- HbA1c demonstrated largest discrepancies in analyses with OM2 vs. OM1.
- A 1% point reduction translated in only 0.06 quality adjusted life year gain (0.1 in OM1).
- We explored the relationship between HbA1c and QALE in lifetime analysis using UKPDS cohort profile and 3% discounting (case study 2 inputs).



Overall QALY gain/1%pt. HbA1c reduction:

OM2: 0.075 quality adjusted life years

OM1: 0.1 quality adjusted life years

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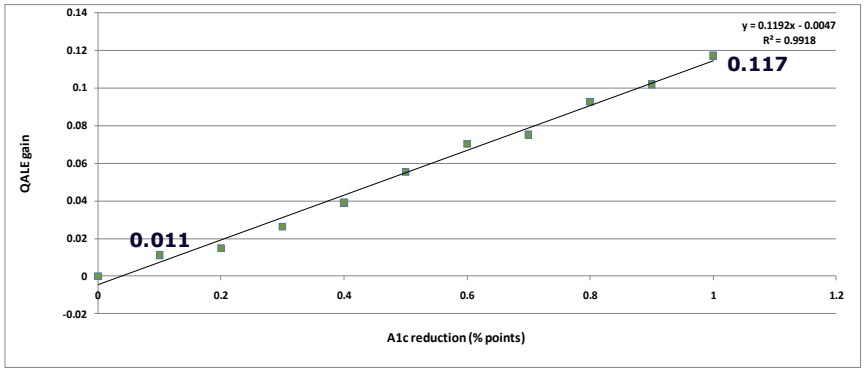
Implications of using UKPDS 82 equations in CEA - 7

Case Study – Overall findings

- ICER change with OM2 equations
  - HbA1c → increase
  - SBP → increase
  - BMI → decrease
  - Multifactorial → almost similar (stronger clinical effect of BMI in OM2)
- Larger ICERs in OM2 analysis driven by incremental QALE (smaller for HbA1c and SBP but bigger for BMI using OM2).
- Incremental costs – only slight differences.
- Life expectancy found to be marginally higher (0.1 year)[3] with OM2 equations.
- 1% point reduction in HbA1c translates into a 0.1 QALY gain using OM1 and 0.06 to 0.075 QALY gain using OM2.



NHANES cohort

3) Foos et al. *Assessing the relationship between the effect of glycemic control and avoided symptomatic hypoglycaemia on quality of life in the management of type 2 diabetes*, ISPOR Berlin, 5th November 2012

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Implications of using UKPDS 82 equations in CEA - 8

Case Study – Causes for differences between OM1 and OM2

Reduced incremental QALE in OM2 vs. OM1

- Cause – Micro vascular complication incidence (FU, AMP, blindness and ESRD)
  - Higher in OM1
  - HbA1c establishes a larger differences in complication rates
  - Which impacts on QALE

Implications of using UKPDS 82 equations in CEA - 9

Conclusions (questions and answers)

- Will there be a consistent trend towards reduced incremental QALE (→ higher ICER)? → No!
  - OM2 equations for ESRD, AMP and blindness will be removed (low incidence avoided HbA1c reduction to translate into QALE difference)
- Is there a predicable trend from OM1 to OM2?
  - No, the impact of the new equations may look different in other input scenarios
- Is the published trend towards lower CV complication incidence with OM2 equations what we will also see in the CDM?
  - No, because OM1 equations in the CDM are applied along with a series of subsequent risk adjustments and therefore produce lower risk scores in comparison to the original OM1 equations
    - Trend in risk score changes from OM1 to OM2:

Validation showed that using OM1 equations in the CDM produces closer matches towards OM2 results vs. published findings.

	Published	CDM
MI	reduced	increased
Stroke	reduced	increased
CHF	reduced	reduced
IHD	reduced	increased
Death	reduced	reduced

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Implications of using UKPDS 82 equations in CEA - 10

Conclusions (questions and answers)

- Do risk factor changes translate differently into value with the new OM2 equations (cost savings, QALE gain)?
  - Mixed scenario
    - HbA1c and SBP → slightly lower gain in incremental QALE.
    - BMI → higher gain in incremental QALE
    - Increased LE with OM2 → more time for risk factor changes to translate into value
    - The role of other cost effectiveness drivers such as hypoglycaemia will remain the same.
- Are differences likely to have a material impact on outcomes or ICERs?
  - It depends…
- Do they have the potential to change a decision based CE thresholds?
  - Unlikely!

Implementation of UKPDS 82 equations in the CDM

Implementation

- Implementation of new OM2 equations into the CDM is not straight forward
  - Verification, Validation and proof of conceptual validity (do equations fit into the model structure)
- The use of the new OM2 equations in the CDM framework will be available with OM1 as option
- IMS will soon release CDM v8.5+ which will…
  - produce consistent outcomes to current version 8.5
  - provide the option to apply OM2 equations.

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