IMS CORE DIABETES USER FORUM

Amsterdam, 9th NOVEMBER 2014
INTRODUCTIONS

IMS CORE DIABETES MODEL DEVELOPMENT TEAM

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  – Senior Principal - Cardiologist, IMS HEOR, Scientific lead of the model.

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  – Senior Principal, IMS HEOR, Commercial lead

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  – Swansea University and Independent Advisor to the IMS CORE Diabetes Model

• Volker Foos vfoos@ch.imshealth.com
  – Senior Consultant - IMS HEOR, main model programmer

• Amélie Beaudet abeaudet@ch.imshealth.com
  – Senior Consultant - IMS HEOR, model trainer and much more

• Francesco Lurati flurati@ch.imshealth.com
  – Applications Specialist – IMS HEOR, IT
<table>
<thead>
<tr>
<th>Item</th>
<th>Presenter</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introductions</td>
<td>Mark Lamotte</td>
<td>14.00</td>
</tr>
<tr>
<td>IMS CDM Version 9.0: - What is new?</td>
<td>Volker Foos</td>
<td>14.05</td>
</tr>
<tr>
<td>- What with type 1 diabetes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee break</td>
<td>All</td>
<td>15.30</td>
</tr>
<tr>
<td>CDM at Mount Hood and EASD</td>
<td>Volker Foos</td>
<td>15.45</td>
</tr>
<tr>
<td></td>
<td>Phil McEwan</td>
<td></td>
</tr>
<tr>
<td>New publications on CDM in Value in Health</td>
<td>Amélie Beaudet</td>
<td>16.05</td>
</tr>
<tr>
<td>- Utilities in diabetes</td>
<td>Phil McEwan</td>
<td></td>
</tr>
<tr>
<td>- Model validation paper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training plans: what will change in the CDM</td>
<td>Amélie Beaudet</td>
<td>16.25</td>
</tr>
<tr>
<td>training?</td>
<td>Phil McEwan</td>
<td></td>
</tr>
<tr>
<td>Questions/comments/feedback?</td>
<td>ALL</td>
<td>16.40</td>
</tr>
</tbody>
</table>
# Abstracts at ISPOR Amsterdam 2014

## Current research with the CDM

<table>
<thead>
<tr>
<th>Day</th>
<th>SESSION I</th>
<th>10 November 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author Discussion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hour</td>
<td></td>
</tr>
<tr>
<td>PDB32</td>
<td>13:15 - 14:15</td>
<td>ASSESSING THE RELATIONSHIP BETWEEN IMPROVED LIFE EXPECTANCY DUE TO BETTER CARDIOVASCULAR RISK FACTOR MANAGEMENT AND THE LIKELIHOOD OF MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS</td>
</tr>
<tr>
<td>PDB29</td>
<td>13:15 - 14:15</td>
<td>PROGRESSION OF PHYSIOLOGICAL PARAMETERS OVER TIME IN TYPE 1 DIABETES MELLITUS PATIENTS IN FRANCE</td>
</tr>
<tr>
<td>PFB61</td>
<td>13:15 - 14:15</td>
<td>BURDEN OF NON-ADHERENCE TO TYPE 1 DIABETES MELLITUS THERAPEUTIC GUIDELINES IN FRANCE</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Day</th>
<th>SESSION IV</th>
<th>11 November 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRM87</td>
<td>18:30 - 19:30</td>
<td>ALL-CAUSE MORTALITY VALIDATION OF THE CORE DIABETES MODEL AGAINST PREDICTIONS OF THE CHARLSON COMORBIDITY INDEX</td>
</tr>
<tr>
<td>PRM23</td>
<td>12:45 - 13:45</td>
<td>IMPACT OF SINGLE RISK FACTOR CHANGES ON LONG TERM OUTCOMES AND COST IN A TYPE 2 DIABETES MODELING STUDY CONTRASTING PROJECTIONS WITH UKPDS 68 VERSUS UKPDS 82 RISK EQUATIONS</td>
</tr>
<tr>
<td>PRM17</td>
<td>12:45 - 13:45</td>
<td>QUANTIFYING NONLINEAR EFFECTS IN STOCHASTIC MARKOV SIMULATION USING UKPDS 68 AND UKPDS 82 EQUATIONS IN TYPE 2 DIABETES MODELING ANALYSIS WITH THE IMS CORE DIABETES MODEL (CDM)</td>
</tr>
</tbody>
</table>
CDM version 9.0 update

- Model back-end (scientific and/or technical updates)
- Model front-end (output section)
THE IMS CORE DIABETES MODEL

UPDATE TO CDM V9.0

- **Scientific updates**
  - New clinical data
  - Modifications to reflect alternative or new assumptions
  - Structural changes that broaden the scientific scope of the model

- **Technical updates**
  - Do not typically change the assumptions in the model (output remains the same)
  - User enhancements
  - Calculation speed/ model capacity/platform

- **Interface enhancements**
  - New outputs
  - New download options
  - Simplification of some aspects of the model (microsimulation and trees taken out, etc.)
  - Any changes related to the CDM interface
THE IMS CORE DIABETES MODEL

UPDATE TO CDM V9.0

- Scientific updates
  1. Hypoglycemia module
  2. Diminishing disutility for NSHE
  3. New CV risk prediction models (alternatively to UKPDS/Fram)
  4. New risk factor progression equations for A1c, BMI, LDL, LR and SBP
  5. Simplification of different sub-models
  6. Update of the T1D section of the model

- Technical updates
  1. Extension of parameters subjected to sampling in PSA: hypo event rates
  2. New option to determine treatment discontinuation based on fixed time
  3. Placeholder sub-models
  4. Platform update to 64 bit
1) Hypoglycaemia module

More detailed approach to consider consequences of hypoglycaemia

- 1) Number of hypoglycemia classifications
  - CDM v9.0
    - NSHE (self manageable)
      - Daytime NSHE
      - Nocturnal NSHE
    - SHE1 (req. 3rd party assistance)
      - Daytime SHE1
      - Nocturnal SHE1
    - SHE2 (requiring med. assistance)
      - Daytime SHE2
      - Nocturnal SHE2
  - CDM v8.5
    - Minor hypoglycemia
      - Daytime
    - Major hypoglycemia
      - Daytime

- 2) Multivariate regression equations
  - Equation 1 for NSHE
  - Equation 2 for SHE

- 3) Costing approach (NSHE, SHE1, SHE2)
  - Direct event costs
  - Indirect event costs

IMS CORE Diabetes User Forum. 9th November 2014
1) Hypoglycaemia module

The costing module (Example for direct costs)

1) We identified resources used to treat hypoglycaemia
2) Frequency by which resources are required to treat NSHE or SHE(1/2)
3) Unit cost for each resource
4) Direct episode costs (sum across all resource items)

<table>
<thead>
<tr>
<th>Resource</th>
<th>SHE (2)</th>
<th>SHE (1)</th>
<th>NSHE</th>
<th>Unit cost</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER visit</td>
<td>17.00%</td>
<td>x 1</td>
<td></td>
<td>$139</td>
<td>$24</td>
</tr>
<tr>
<td>Ambulance</td>
<td>21.32%</td>
<td>x 1</td>
<td></td>
<td>$214</td>
<td>$46</td>
</tr>
<tr>
<td>Inpatient</td>
<td>0.00%</td>
<td>x 1</td>
<td></td>
<td>$4,171</td>
<td>0</td>
</tr>
<tr>
<td>Inpatient with ER</td>
<td>24.00%</td>
<td>x 1</td>
<td></td>
<td>$4,171</td>
<td>$1'001</td>
</tr>
<tr>
<td>Outpatient</td>
<td>20.00%</td>
<td>x 1</td>
<td></td>
<td>$285</td>
<td>$57</td>
</tr>
<tr>
<td><strong>Primary Care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to GP</td>
<td>26%</td>
<td>x 1</td>
<td></td>
<td>$51</td>
<td>$13</td>
</tr>
<tr>
<td>Home visit from GP</td>
<td>0%</td>
<td>x 1</td>
<td></td>
<td>$59</td>
<td>0</td>
</tr>
<tr>
<td>Nurse</td>
<td>13.00%</td>
<td>x 1</td>
<td></td>
<td>$43</td>
<td>$6</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non HCP treatment (self Tx or 3rd party assistance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra SMBG tests</td>
<td>3.9</td>
<td></td>
<td></td>
<td>$0.98</td>
<td>$4</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1,150</td>
</tr>
</tbody>
</table>

Results (Direct US episode costs)

- SHE 2: $1,150
- SHE 1: $66
- NSHE: $11

References

Frequency of resources


US unit costs for resources

- Medicare 2012 Physician Fee Schedule
- Medicare "Outpatient Prospective Payment System" (OPPS)
- Medicare "Inpatient Prospective Payment system" (IPPS)
- Medicare ambulance fee schedule

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IMS CORE Diabetes User Forum. 9th November 2014
1) Hypoglycaemia module

**NSHE - Log-linear regression model**

- Literature review: Data were extracted from 82 insulin bases clinical trials for a total of 155 trial arms!
- Log-linear regression indicated that many variables were highly significant

|                          | Coefficient | SE   | Z    | P(>|z|) |
|--------------------------|-------------|------|------|---------|
| Intercept                | 14.771      | 1.740| 8.49 | <0.001  |
| Baseline age             | -0.088      | 0.021| -4.11| <0.001  |
| Baseline HbA1c           | -0.667      | 0.148| -4.50| <0.001  |
| HbA1c reduction          | 0.427       | 0.143| 2.98 | <0.01   |
| Duration of diabetes     | 0.189       | 0.035| 5.33 | <0.001  |
| % allowed SU             | 0.007       | 0.002| 3.57 | <0.001  |
| Basal analog used        | -0.545      | 0.175| -3.11| 0.002   |

\[
\text{NSHE/100PY} = \exp(14.771 - 0.088 \times \text{age} - 0.667 \times \text{baseline HbA1c} + 0.427 \times \text{HbA1c reduction} + 0.189 \times \text{duration diabetes} + 0.007 \times \% \text{ study allowed sulphonylurea} - 0.545 \times \text{basal analog insulin})
\]

1. McEwan et al. Predicting the frequency of severe and non-severe hypoglycaemia in insulin treated type-2 diabetes subjects. Presented at the ISPOR 16th Annual European Congress, Dublin 2-6 November 2013
1) Hypoglycaemia module

**SHE - Log-linear regression model**

- Log-linear regression indicated that many variables were highly significant
- Includes SHE1 and SHE2
- 11.8% are considered SHE2

| Coefficient | SE    | Z    | P(>|z|) |
|-------------|-------|------|--------|
| Intercept   | 10.794| 2.036| 5.30   | <0.001 |
| Baseline age| -0.101| 0.025| -4.12  | <0.001 |
| Duration of diabetes | 0.163 | 0.039 | 4.21   | <0.001 |
| Baseline HbA1c | -0.723| 0.173| -4.17  | <0.001 |
| HbA1c reduction | 0.638 | 0.166| 3.85   | <0.001 |
| Biphasic Insulin  | 0.768 | 0.312| 2.44   | 0.015  |

\[ \text{SHE/100PY} = \exp(10.794 - 0.101 \times \text{age} - 0.723 \times \text{baseline HbA1c} + 0.638 \times \text{HbA1c reduction} + 0.163 \times \text{duration diabetes} + 0.768 \times \text{biphasic insulin}) - 1 \]

1-McEwan et al. Predicting the frequency of severe and non-severe hypoglycaemia in insulin treated type-2 diabetes subjects. Presented at the ISPOR 16th Annual European Congress, Dublin 2-6 November 2013
2) Diminishing disutility for NSHE

Integration of non-linear approach to evaluate NSHE disutility

- Until CDM v8.5 a static approach was applied to consider the impact of NSHE on HRQOL
  - 1 NSHE event per year → disutility of -0.0052
  - 10 NSH events per year → disutility = 10 x -0.0052 = 0.052

- **The trend of diminishing NSHE annual disutility** was reported in two independent studies
  - Acknowledgement of phenomenon:
    - If patients experience > 1 events during one year, the impact of the “1st event is the worst”
    - *Thereafter*, the negative impact of each NSHE **declines** (diminishes) as the frequency increases.
  - Two independent studies:
    - Large TTO study of >8000 respondents from five countries (UK, USA, Canada, Germany and Sweden) (1)
    - Data from postal survey of 1305 respondents from the UK (2)

2) Diminishing disutility for NSHE

Static vs. Diminishing approach

![Graph showing the comparison between nocturnal and daytime disutility for NSHE using static and diminishing approaches.]

Nocturnal NSHE disutility of -0.007 (3)
Daytime NSHE disutility of -0.004 (3)

Poster at ISPOR, Montreal (2014)
- Implications of using static vs. diminishing approach in the CDM
- Download available at CDM website

3) New CVD risk prediction models

Background

- A series of cardiovascular (CV) risk equations were published recently and the potential choice of risk equations (RE) is large.

- Many economic models use RE derived from UKPDS and concerns persist regarding their validity.
  - UKPDS equations are built on data that is becoming out of date
  - UKPDS were managed differently and treatment pathways have changed since the study was initiated.
  - UKPDS data are based on a UK population. What with other populations?

- HTA bodies want more justification that the model outputs are credible.

- A recent investigation with the CDM (4) compared the consistency and predictive nature of 12 risk equations described in a recent review (5).

3) New CVD risk prediction models

Interim analysis suggesting UKPDS based RE perform “on average” vs. contemporary RE from other sources

Conclusion

- **UKPDS** equations produced CV risk estimates close to group averages
- The difference in absolute risk across equations does not appear dependent on geographical location
- Where possible, economic evaluations in T2DM should conduct sensitivity analysis across multiple equations
- **IMS** will consider the integration of additional risk equations with respect to
  - Geographical region (cover the most important regions such as US, Europe, Asia)
  - Modeled end points suitable for integration into the CDM

3) New CVD risk prediction models

**NEW CVD risk prediction models for CDM v9.0 update**

<table>
<thead>
<tr>
<th>Europe/Nordics</th>
<th>Multy country*</th>
<th>Asia</th>
<th>US</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish NDR (2013)</td>
<td>ADVANCE* risk engine</td>
<td>Procam</td>
<td>Hong Kong Registry</td>
<td>ARIC</td>
</tr>
<tr>
<td>1st MI</td>
<td>MI or stroke composite</td>
<td>Coronary artery disease = fatal and nonfatal MI, PCI or CABG</td>
<td>CHD</td>
<td>CHD = MI or CHD death or CABG</td>
</tr>
<tr>
<td>2nd MI</td>
<td></td>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>1st Stroke</td>
<td></td>
<td></td>
<td>HF</td>
<td></td>
</tr>
<tr>
<td>2nd Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Multy country trial involving 215 centers in 20 countries from Asia, Australia, Europe and North America.

10) Yang X et al. Diabetes Care 2007 30:65–70
11) Yang X et al. Cardiovascular Diabetology 2008, 7:9
4) Risk factor progression equations (Swedish NDR)

Equations for HbA1c, SBP, BMI, TC : HDL, and LDL

- The **key aspect** of risk modeling is the **understanding** of how **risk factors** change over time.
- The **UKPDS 68** study is the **main source** of predicting changes in risk factors over time and is widely used in diabetes models.
- **New equations** derived from the Swedish NDR (14) will be made available as alternative approaches.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>UKPDS 68</th>
<th>Framingham</th>
<th>Table (static)</th>
<th>S-NDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>SBP</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_Chol</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>HDL</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No convergence

Parameters converge over time

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5) SIMPLIFICATION OF SUB-MODELS

Revision of the Microvascular section

• The CDM has 19 submodels

• Most of them were created 10 years ago and the medical practice has evolved since then.

⇒ An update of some of the microvascular submodels is needed
  – Nephropathy: use of ACE-inhibitors
  – Proliferative retinopathy: screening
  – Macular oedema: new therapies are available
  – Foot ulcer: detail on next slides

• Main purposes
  – To make populating the model easier
  – Be close to daily practice
5) Foot ulcer sub-model

The foot ulcer sub-model will be simplified

Modifications

- Structure will be simplified
- Sub-states reduced (from 9 to 5)
- Cycle length adapted (from monthly to yearly)
- Cost collection simplified and more in line with clinical practice
- UKPDS equations will be applied for transition probabilities
### 5) Foot ulcer sub-model

Foot ulcer costs in existing Economic setting will be converted.

<table>
<thead>
<tr>
<th>Current model</th>
<th>Weight</th>
<th>New model</th>
</tr>
</thead>
<tbody>
<tr>
<td>c after healed ulcer</td>
<td></td>
<td>Not used in the new model</td>
</tr>
<tr>
<td>c Gangrene treatment</td>
<td>31%</td>
<td>Converted to &quot;c Foot ulcer&quot;</td>
</tr>
<tr>
<td>c standard uninfected ulcer</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>c infected ulcer</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>c Amputation (event based)</td>
<td></td>
<td>Will be kept</td>
</tr>
<tr>
<td>c Amp Prosthesis (event based)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c healed ulcer history of amputation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Foot ulcer costs for gangrene, uninfected and infected ulcer will be **weighted** according to their expected proportions.

Proportions were obtained from the **Eurodiale study** (multi-country study including 1300 cases of foot ulcer reported in 14 European hospitals).

**Reference**
6) Type 1 diabetes

- Current stand and new features
6) Type 1 Diabetes update – current version

Bootstrap Simulation → No sampling → 2nd order with sampling → Patient level data analysis → Sample input parameters → Baseline Cohort → Microsimulation

Baseline Cohort → 1st patient to run → Patient alive? → Time horizon reached? → Stop!

Patient alive? → No → Stop! → YES → Time horizon reached?

T1DM considerations:
- Type 1 data applied
- Type 2 data applied
- Data not type specific
- Not applied in T1DM

Hypoglycemia module

T1DM considerations:
- Type 1 data applied
- Type 2 data applied
- Data not type specific
- Not applied in T1DM

Specific Mortality → MI → Angina → CHF → Stroke → PVD → Respiratoryopathy

Specific Mortality → Uric/Amputa → Retinopathy → Macular Edema → Cataracts → Neuropathy → Depression → Hypoglycemia → Ketoacidosis → Lactic acidosis → Edema → Non-spec. Mort

Specific Mortality → ACE/ARB treatment → Statin treatment → Aspirin treatment → Laser treatment → Screening → Smoking

Stop → YES → Did patient die? → Time counter advances → Run Treatment algorithm → Update simulation data

N Patients → B Bootstrap iterations

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# 6) Type 1 Diabetes update

Data sources applied to microvascular disease (current)

<table>
<thead>
<tr>
<th>Eye disease</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transition probabilities</strong></td>
<td></td>
</tr>
<tr>
<td>BDR</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>BDR-PDR</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>PDR-SVL</td>
<td>Javitt²</td>
</tr>
<tr>
<td>ME</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>ME-SVL</td>
<td>DCCT¹</td>
</tr>
<tr>
<td><strong>Risk factors &amp; adjustments</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment type (intensive/conventional)</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>Prim. prev. vs. sec. interv.</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>• Duration of diabetes (&lt;5)</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>• Renal disease state</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>• Eye disease state</td>
<td>DCCT¹</td>
</tr>
<tr>
<td>HbA1c</td>
<td>DCCT³</td>
</tr>
<tr>
<td>SBP</td>
<td>UKPDS</td>
</tr>
<tr>
<td>ACE</td>
<td>Malik⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal disease</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transition probabilities</strong></td>
<td></td>
</tr>
<tr>
<td>MAU</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>MAU-GRP</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>GRP-ESRD</td>
<td>Javitt²</td>
</tr>
<tr>
<td>ESRD death</td>
<td>DCCT¹</td>
</tr>
<tr>
<td><strong>Risk factors &amp; adjustments</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment type (intensive/conventional)</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>Prim. prev. vs. sec. interv.</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>• Duration of diabetes (&lt;5)</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>• Renal disease state</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>• Eye disease state</td>
<td>DCCT⁵</td>
</tr>
<tr>
<td>HbA1c</td>
<td>DCCT³</td>
</tr>
<tr>
<td>SBP</td>
<td>UKPDS</td>
</tr>
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<td>ACE</td>
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<td>Reversal (set to 0)</td>
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<td><strong>Risk factors &amp; adjustments</strong></td>
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<td>Treatment type (intensive/conventional)</td>
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<td>Prim. prev. vs. sec. interv.</td>
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<td>• Duration of diabetes (&lt;5)</td>
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<td>• Renal disease state</td>
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<td>• Eye disease state</td>
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</table>

3 - The DCCT Research Group; Diabetes 1996;45:1289-98
8 - The DCCT Research Group; Ann Intern Med 1995;122:561-8
6) Type 1 Diabetes update

2014 Revalidation results

- Internal validation (DCCT$^1$)
  - Close match as expected

- External validation (EDIC$^2$)
  - Acceptable
  - Slight overestimation of ESRD
  - Underestimation of CV death
  - Difference between intensive and conventional therapy less pronounced in CDM

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6) Type 1 Diabetes update

Microvascular updates
6) Type 1 Diabetes update

Microvascular updates

Revision of findings from the EDIC study\(^1\). Data will be included in CDM if applicable

6) Type 1 Diabetes update

Microvascular updates

Revision of findings from the **EDIC study**. Data will be included in CDM if applicable


Cohort study\(^3\):
- 20K T1D individuals
- Finnish Diabetes Register
- ESRD incidence

3. Finne P et al. JAMA, October 12, 2005—Vol 294, No. 14
6) Type 1 Diabetes update

Microvascular updates

Revision of findings from the **EDIC study**. Data will be included in CDM if applicable


2. Finne P et al. JAMA, October 12, 2005—Vol 294, No. 14


Cohort study\(^1\):
- 31K T1D individuals
- S-NDR
- AMP incidence

Cohort study\(^3\):
- 20K T1D individuals
- Finnish Diabetes Register
- ESRD incidence
6) Type 1 Diabetes update

Cardiovascular Disease - Updates
6) Type 1 Diabetes update

Cardiovascular Disease - Updates

- Pittsburgh CHD study (1)
- CHD RE for T1D

6) Type 1 Diabetes update

Cardiovascular Disease - Updates

- Pittsburgh CHD study (1)
- CHD RE for T1D
- Pittsburgh CHD study (2)
- CHD RR adjustment (T1D vs. T2D)
- CDM clinical setting

6) Type 1 Diabetes update

Cardiovascular Disease - Updates

- Pittsburgh CHD study (1)
- CHD RE for T1D

- Pittsburgh CHD study (2)
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- S-NDR
- Analysis of 3661 T1D individuals
- RE for 5-yr risk of CVD

6) Type 1 Diabetes update

Cardiovascular Disease - Updates

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- S-NDR
- Analysis of 3661 T1D individuals
- RE for 5-yr risk of CVD

- WA-hospital and mortality records from T1D and T2D
- T1D specific mortality RE (3)

6) Type 1 Diabetes update

Cardiovascular Disease - Updates

• Pittsburgh CHD study (1)
• CHD RE for T1D

• Pittsburgh CHD study (2)
• CHD RR adjustment (T1D vs. T2D)
• CDM clinical setting

• S-NDR
• Analysis of 3661 T1D individuals
• RE for 5-yr risk of CVD

• WA-hospital and mortality records from T1D and T2D
• T1D specific mortality RE

• Prospective study (Finland)
• Incl. 173 T1D and 834 T2D
• 18 yr follow up
  → RR CVD mortality

6) Type 1 Diabetes update

Cardiovascular Disease - Updates

- Pittsburgh CHD study (1)
- CHD RE for T1D
- Pittsburgh CHD study (2)
- CHD RR adjustment (T1D vs. T2D)
- CDM clinical setting
- S-NDR
- Analysis of 3661 T1D individuals
- RE for 5-yr risk of CVD

- 14K hospital and mortality records from T1D and T2D in WA
- T1D specific mortality RE

- Prospective study (Finland)
- Incl. 173 T1D and 834 T2D
- 18 yr follow up → RR CVD mortality

- S-NDR
  - HR CV mortality post SHE
  - HR = 1.75 (<1mth)
  - HR = 1.25 (>1mth)

6) Type 1 diabetes update

The literature review for the T1D update is not completed

- The T1D model update in the CDM is still under review
- We may add additional data/risk engines after review of available sources in the public domain
- Candidate papers for consideration are:
  - Review of a recently published T1D simulation model\textsuperscript{10}
  - Review of the Sheffield Type 1 Diabetes Policy Model\textsuperscript{11}

- Additional updates
  - Treatment algorithms in T1D
    - Allow assumptions of changing insulin regimens over the course of the disease.
    - Pilot studies focusing on using GLP1/DPP4 in T1D
      - to reduce insulin dose
      - to minimize hypo risk
  - T1D specific progression equations
    - Dataset comprising 605 T1D individuals from IMS LifeLink Diabetes Cohort in France\textsuperscript{12}
    - Data available for HbA1c, SBP, BMI and lipids

\textsuperscript{10} Lung TW et al. PharmacoEconomics (2013) 31:509–518
\textsuperscript{11} Thokala P. Diabet Med. 2014 Apr;31(4):477-86
\textsuperscript{12} Beaudet et al. ISPOR, Amsterdam, 8-12 November 2014 | PDB29
CDM version 9.0 update

Technical updates

- Additional outputs in the CDM
  1. Extension of parameters subjected to sampling in PSA: hypo event rates
  2. New option to determine treatment discontinuation based on fixed time
  3. Placeholder sub-models
  4. Platform update to 64 bit
Technical updates

Placeholder sub-models to track medication specific adverse events

1. Placeholder sub-models
   - Edema and lactic acidosis sub-models not used in CDM anymore
   - Those sub-models will be converted to generic placeholders
     - Adverse event 1
     - Adverse event 2
   - Sub-models should have no implications in standard runs (zero incidence, costs and benefits) but may be used to incorporate assumptions related to specific drug related adverse events or other complications of diabetes.
   - Event rates editable in treatment settings.
   - Costs and utility data will be renamed accordingly in the specific sections (Economics, Clinical)

2. Event rates for hypoglycemia (NSHE, SHE1 and SHE2) will be subjected to sampling in PSA
Technical updates

Placeholder sub-models to track medication specific adverse events

3. New option to specify time of treatment discontinuation
   • Option 1 – based on HbA1c threshold
   • Option 2 – based on treatment failure probabilities for first five years
   • **Option 3 – New**: Treatment duration can be defined numerically (e.g. 23 years)

4. Treatment trees will be removed

5. Platform upgrade
   • Front end redevelopment (ASP.NET)
   • Back end redevelopment (64 bit upgrade)
CDM version 9.0 update

Model front-end

- Additional outputs in the CDM
  1. Cumulative QALE over time
  2. Time to treatment escalation (TTE)
  3. Incidence of secondary CVD events (2nd MI and 2nd stroke)
  4. Option to export individual sample outcomes in PSA
1) Cumulative QALE over time

Present cumulative QALE over time

- Applied in recent research\(^1\) to understand the attenuating effect of discounting on benefits achieved from glucose lowering vs. avoidance of symptomatic hypoglycemia.
- Important feature to understand underlying processes in the modeling
- Implications on QALE following treatment changes (e.g. due to hypoglycaemia) can be tracked.

\(^1\) Foos et al. Assessing the relationship between the effect of glycemic control and avoided symptomatic hypoglycemia on quality of life in the management of type 2 diabetes, ISPOR 15th Annual European Congress, Berlin, Germany, November 3-7, 2012| DB1
2) Time to treatment escalation (TTE)

Time to treatment escalation (TTE)

- Assumptions to treatment escalation in T2D have considerable effects on cost effectiveness outcomes
- TTE is commonly determined by
  - HbA1c escalation threshold
  - HbA1c trajectory over time (durability)
- Dependent on the costs of escalation therapy, TTE can represent a strong cost effectiveness driver.
- TTE cannot be assessed in analyses that apply 2nd order parameter sampling
- TTE is therefore an important variable to study.

**Figure**

- Illustrates the impact of sampling vs. no sampling of baseline HbA1c on average time to treatment escalation (ATTE) and the proportion of patients remaining on 2nd line regimen over time (before tx change)\(^2\).

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\(^2\) Mc Evan et al. Therapy escalation thresholds and the potential for biased cost effectiveness analysis when failing to sample baseline HbA1c in type 2 diabetes, ISPOR 16th Annual European Congress, Dublin, 2-6 November 2013 | PRM98
3/4) Other output enhancements

Other interface and output enhancements

3. Cumulative incidence of secondary events (2nd MI, 2nd Stroke)

4. Option to export individual sample outcomes in PSA
   - Enable comparison of input- vs. output profiles to enable sub-group analysis (similar to PLD analysis)

5. Color indication of default settings in CDM input modules
   - CDM input settings (Treatment, Cohort etc.) will be indicated by different colors to differentiate:
     - Inputs that are typically collected within the scope of a CDM cost effectiveness analysis
       - Treatment efficacy on HbA1c, SBP etc.
     - Inputs that are more likely to remain at the default level
       - RR for 1st MI
       - RR for 1st stroke
       - Apply risk adjustment for statins?
       - Apply risk adjustment for ACE?
WEBSITE AND ACCESS TO THE MODEL

FRONT END MODIFICATINOS

• CDM website will be incorporated in global IMS website
  – Current link will be directed to IMS website
  – No information will be lost
  – Log in page remains

• Access to the model will be linked to an e-mail address
  – IMS is not aware of users leaving their job
  – Automatic e-mails will be send to your e-mail address to confirm password
CDM at Mount Hood and EASD
CDM at Mount Hood

Stanford University in Palo Alto, CA

- **MT Hood challenge**
  - Forum for computer modelers of diabetes to
    - **Compare** and discuss **models**
    - **Cross validate** models against data from clinical trials and other studies (RWE)
    - **Identify** key future **developments** in the **field**.
  - Six previous MT Hood meetings have been held since the 1st in 1999 at MT Hood in Oregon

- **Theme of the 2104 challenge**
  - How to generalize diabetes models for different populations
  - To what degree are models able to adjust for differences in risk due to ethnic and socio-economic differences
CDM at Mount Hood

Stanford University in Palo Alto, CA

- Conference consisted of three ‘challenges’
  1. Replication of key endpoints from the Action for Health Diabetes (Look AHEAD)
  2. Predicting mortality following first myocardial infarction and 1st stroke
  3. Variation in event rates due to ethnicity

- A manuscript will be developed detailing the results of the challenges
  - Until then, no results can be shared or discussed
  - We would like to give some more background to the ultimate rationale and motivation to undertake these challenges.
  - Present how the CDM was equipped to undertake these challenges.
CDM at Mount Hood

Challenge I – LOOK AHEAD VALIDATION

• LOOK AHEAD TRIAL
  1. Included 5145 overweight or obese T2D individuals
     1. Intensive lifestyle intervention (weight reduction 8.6%, HbA1c -0.6% points)
        1. Decreased caloric intake
        2. Physical activity
     2. Diabetes support and education (weight red.0.7%, HbA1c -0.1% points)
  2. Results
     1. Trial was stopped at median follow-up was 9.6 years.
     2. No significant differences were observed in the primary outcome (CV incidence and death)
     3. Weight loss did not reduce the rate of CV events in overweight T2D individuals.

• A systematic review\(^1\) on diabetes simulation models was recently published.
  • Authors claimed that models make fundamental assumptions related to weight effects that are too strong and not supported by the literature.
  • In the CDM, BMI is incorporated in CV-risk equations (HF only!) that are derived from UKPDS
  • Most other participating models utilize the same equations.
  • The impact of weight (or BMI) changes on outcomes is modest.

\(^1\) Asche CV, Hippler SE, Eurich DT. Pharmacoeconomics. 2014 Jan;32(1):15-27
CDM at Mount Hood

Challenge I – LOOK AHEAD Validation

• Example – impact of BMI changes
  • ACCORD like population
  • One unit reduction of BMI from 32 to 31 Kg/m2 (over life time)
    • → 0.008 life years gained (3 days)
    • → 0.004 QALYs gained (no BMI adjustment for QALE)
    • 4.5% relative reduction of HF incidence (16.1% vs. 16.8%).

• External validation of LOOK AHEAD is important to help eliminate doubts that models overestimate the clinical effects associated with weight changes
CDM at Mount Hood

Challenge II – Mortality Validation

- It is important to understand how models are capable of predicting mortality across populations
- Understand to what degree improvements in diabetes care are considered by models
- Validation challenge:
  - Compare 5 year mortality following MI (a) and stroke (b) to observations in 20,836 people with T2DM from the Swedish National Diabetes Register.

- We cannot present results of the mortality validation against S-NDR data, but
- Would like to present some general research with the CDM around this topic.
CDM at Mount Hood

Challenge II – Mortality Validation

- A CDM validation study is presented at ISPOR conference (1) to contrast CDM validation outcomes when the model is compared to
  - A) RCTs (incl. ACCORD, ADVANCE, ASPEN)
  - B) Data aligned to non-controlled, real-world observations

  **Charlson Comorbidit Index**
  - CCI is a widely utilized index tool to measure the burden of disease and predict mortality in various disease subgroups

  **The UK General Practice Research Database (GPRD)**
  - Retrospective cohort study (7) from the GPRD to compare patients treated with

  **Life expectancy calculator** based on administrative dataset from Western Australia (WA-LEC)
  - LE calculator applies risk equations derived from 13,884 Western Australian hospital and mortality records
CDM at Mount Hood – Challenge III

Ethnicity differences

- **Goal of challenge**
  - Estimate survival, costs and diabetes-related outcomes for an average T2DM profile and all ethnic groups considered in the respective models.

- **General considerations** – why is ethnic differentiation important?
  - Ethnicity can considerably influence the incidence of diabetes-related complications
  - Causes are genetic, socioeconomic and socio-cultural factors
  - Accounting for the heterogeneity of the treated population to identify subgroups is important to expose variation in incremental cost-effectiveness ratios (ICERs)
  - Important to understand the extent to which models consider ethnic differences
## CDM at Mount Hood – Challenge III

### Ethnicity adjustments in the CDM

#### Microvascular

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Ethnicity risk associations published in a systematic review

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**Nephropathy & ESRD**

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**CV complications**

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**Neuropathy**

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**Mortality**

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</table>

- Review published in Diabetes Care in 2006
- Review comprised 56 studies on ethnicity related risk associations to diabetes related complications
- Qualitative review counting...
- Similar trend of ethnicity-related risk associations for renal disease, eye disease, CV disease and mortality, is revealing.
CDM at Mount Hood – Challenge III

Ethnicity differences

- A comparison of ethnic adjustments in the CDM to a systematic review

<table>
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<tr>
<th>Microvascular</th>
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<td>x</td>
<td>1.01</td>
<td>1.06</td>
<td>1.07</td>
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<tr>
<td></td>
<td>T1DM &amp; T2DM</td>
<td>x</td>
<td>1.01</td>
<td>1.07</td>
<td>1.22</td>
<td>x</td>
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</table>

| Renal disease | T2DM       | x     | 1.32   | 1.17     | 1.00            | x                      | x      |
|               | T1DM       | x     | 1.01   | 1.07     | 1.22            | x                      | x      |
|               | T1DM & T2DM| x     | 1.01   | 1.07     | 1.22            | x                      | x      |
|               | ESRD death | x     | 0.72   | 1.01     | 1.00            | x                      | x      |

| Neurology     | T2DM       | x     | 0.56   | 1.07     | 1.00            | x                      | x      |
|               | T1DM       | x     | 1.00   | 1.07     | 1.22            | x                      | x      |
|               | T1DM & T2DM| x     | 1.00   | 1.07     | 1.22            | x                      | x      |

| Macrovascular | T2DM & T2DM| x     | 0.63   | 1.07     | 1.00            | x                      | x      |

| MI            | T2DM & T2DM| x     | UK 88 RF | UK 88 RE | UK 88 RF | x                      | x      |
| Stroke        | T2DM & T2DM| x     | x       | x        | x        | x                      | x      |
| IHD           | T2DM & T2DM| x     | x       | x        | x        | x                      | x      |
| CHF           | T2DM & T2DM| x     | x       | x        | x        | x                      | x      |

| Mortality     | T2DM & T2DM| x     | x       | x        | x        | x                      | x      |

 IMS CORE Diabetes User Forum. 9th November 2014
CDM publications in 2014

- Validation of the CDM v8.5+
- Review of utility values
**Objectives**
- The objective was to identify a set of utility values consistent with NICE reference case and to critically discuss and illustrate challenges in creating such a utility set.

**Methods**
- A systematic literature review was conducted.
- The methodology of each study was assessed for consistency with the NICE reference case.
- A suggested set of utility values applicable to modeling was derived, giving preference to studies reporting multiple complications and correcting for comorbidity.

**Results**
- Index value estimates for T2DM without complication ranged from 0.711 to 0.940.
- Utility decrement associated with complications ranged from 0.014 (minor hypoglycemia) to 0.28 (amputation).
- Limitations included variability inpatient recruitment, heterogeneity in statistical analysis, large variability around some point estimates, and lack of recent data.
Fig. 2 - BMI, body mass index; Cl, confidence interval; DR, diabetic retinopathy; T2DM, type 2 diabetes mellitus.
Model Validation

Validation in 2004 and 2014
Model Validation - 2004

- The model has been previously validated in 2004
  - Total of 66 second- (internal) and third- (external) order validation analyses
  - Correlation analysis (study outcome vs. model prediction) showed good fit
    - Overall fit: $R^2 = 0.9224$
    - T1DM: $R^2 = 0.9778$
    - T2DM: $R^2 = 0.8861$

Then the model took part in all Mount Hood Challenges
Model Validation - 2013

- The current version (8.5) of the CORE model has also been validated

- Objective
  - To validate the CORE model to contemporary outcomes data; particularly those with a 20-30 year time horizon (long term)

- Approach
  - Validation output was assessed across 112 endpoints from treatment arms of nine pivotal T1DM and T2DM studies
  - From these nine studies, endpoints used for validation testing were stratified by duration of study follow-up into two types of validations
    - Intermediate-term validations:
      DCCT; UKPDS 33; ASPEN; VADT; ADVANCE; ACCORD; ADDITION-Europe; ASCOT; CARDS
    - Long-term validations:
      DCCT/EDIC for T1DM and UKPDS for T2DM
CORE Diabetes Model Validation results (2014)

- Each chart shows excellent fit, whether by year, study, endpoint, or diabetes type

- Overall goodness-of-fit ($R^2$) was high, at 0.90

- No evidence of systematic lack-of-fit

- ACCORD (Glucose lowering) validations indicated lack of fit
CORE Diabetes Model Validation results (Continued)

- Presented by validation and diabetes type

- $R^2$ of 0.93 and 0.80 for internal and external validation

- For long-term T1DM (DCCT/EDIC 17-30 years) studies, $R^2$ was 0.72

- For long-term T2DM (UKPDS 20 years) studies, $R^2$ was 0.92
Training Plans

What will change..
Training approach

- Current approach uses a mix of case studies to describe how to set up and run the CDM
- Interspersed with illustrations of why things are implemented the way they are.
- Key improvements proposed
  - Offer pre-training reading and a test post training.
  - The presentation of drivers of cost effectiveness in the CDM
  - Develop an understanding of how the model works with respect to these key drivers
  - Which input parameters are really important
  - How do you validate model applications
  - Case studies built around these key drivers
Training deliverables

• General education component delivered via a mix of presentations and interactive workbooks.

• Position statements regarding approaches to model settings and areas where agreement on modeling approaches not universally agreed
  – Sampling parameters, run time, BMI trajectories, LDL, eGFR

• Interactive workbooks (switch to Excel)
Drivers of cost effectiveness

Baseline HbA1c and therapy escalation and sampling

- Higher baseline HbA1c = faster time to therapy escalation
- Treatment effects often applied independently of baseline HbA1c

Vienna 15th September 2014
Comparing HbA1c and weight change as drivers of cost effectiveness

- **HbA1c reduction (top graph)**
  - 15 year cumulative incidence of stroke and MI for HbA1c of 7.5% versus 8.5%
  - Total QALY difference per 1000 patients: 39 QALYs

- **BMI change (bottom graph)**
  - Comparing 2kg weight loss versus 2kg weight gain
  - Weight loss reversed at year 5
  - Total QALY difference per 1000 patients: 76 QALYs

- **BMI provides more health economic benefit – related to quality of life, not avoided complications!**
CDM Interactive Tool

Tool to interactively explore the directions and trends in the CDM

The IMS CORE Diabetes Model, the most widely used economic model for HTA submissions in diabetes.

Validation
Cost Effectiveness Forcaster
Run Time Requirement in PSA
Endpoint Stabilization
Other...

Validations across selected study cohorts can be interactively reviewed while CDM input assumptions are modifiable.

View cost effectiveness scenarios for selected cohort profiles, interactively change modifiable CDM input assumptions, intervention effects and treatment costs.

Research leading to IMS recommendations for minimum run time requirements (RTR) in probabilistic sensitivity analysis (PSA).

Research leading to IMS recommendations for minimum RTR in standard base case analysis for end point predictions.

Table of contents with a brief descriptions of the various sections within the hypoglycemia module.
IMS CORE Diabetes Model User Forum
Questions/comments/feedback?
Thank You!