

UKPDS Outcomes Model

User Manual

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Produced by the University of Oxford

Diabetes Trials Unit (DTU) and

Health Economics Research Centre (HERC)

www.dtu.ox.ac.uk/outcomesmodel

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To obtain a copy of the UKPDS Outcomes Model[®] software and a license to use it, please contact:

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For all queries concerning the UKPDS Outcomes Model[®] and its appropriate use please read this manual and the web site FAQ (www.dtu.ox.ac.uk/outcomesmodel).

If your question concerning the use of the software remains unanswered, email herc@dph.ox.ac.uk. **Please note that general questions regarding diabetes simulation modelling, e.g. whether particular assumptions made by the user are appropriate, cannot be accepted.**

For purely technical enquiries concerning software installation, email outcomes.model@dtu.ox.ac.uk.

Background

The UKPDS Outcomes Model[®] is a computerised simulation tool designed to estimate Life Expectancy, Quality Adjusted Life Expectancy and the cumulative costs of complications in people with type 2 diabetes mellitus (T2DM). It uses the peer-reviewed equations and algorithms published in the UK Prospective Diabetes Study (UKPDS) paper 82,¹ which should be read prior to using this software.

Caution should be applied if model results are extrapolated to populations that differ significantly from that included in the UKPDS, or that include ethnic groups other than White Caucasian, Afro-Caribbean or Asian-Indian.

The model was developed using data from patients with newly-diagnosed type 2 diabetes who participated in the UKPDS.² Version 1 of the UKPDS Outcomes Model[®] (OM1) incorporated equations for forecasting the occurrence of seven diabetes-related complications (ischaemic heart disease, chronic heart failure, first amputation, blindness in one eye, renal failure, first stroke, first myocardial infarction) and death. These were estimated using data from 3642 UKPDS patients with complete information on risk factors and outcomes.³ Version 2 of the UKPDS Outcomes Model[®] (OM2) uses data from all 5,102 UKPDS patients who entered the trial and the 4,031 survivors who entered the 10 year post-trial monitoring period.

The equations in OM2 are based on median 17.6 years of follow-up with 89,760 patient-years of data, providing double the number of events available when OM1 was developed to give greater precision and a larger number of significant covariates. These data were used to derive parametric proportional hazards models predicting absolute risk of diabetes complications and death.¹

The additional follow-up data allowed the seven original event equations to be re-estimated and to be supplemented with equations for 4 more complications, *i.e.* diabetic ulcer, second amputation, second stroke and second myocardial infarction, as well as the development of four new equations for all-cause mortality.¹

Internal validation of model predictions of cumulative incidence of all events and death was carried out and a contemporary patient-level dataset was used to compare 10-year predictions from OM1 and OM2. OM2 is internally valid over 25 years, and predicts event rates for complications which are lower than those from OM1.

OM1 incorporated risk factor trajectory equations that forecasted changes over time in smoking status, total cholesterol, HDL-cholesterol, systolic blood pressure and HbA_{1c}. Updated equations have been estimated for these five risk factors, as well as trajectory equations for 8 more risk factors, *i.e.* peripheral vascular disease, atrial fibrillation, weight, albuminuria, heart rate, white blood cell count, haemoglobin and eGFR. However, these updated equations will not be incorporated into OM2 until they have been validated and fully published; until then, users may paste in their own data, or use one of the built in methods for populating the values: that is, hold the initial values constant for the simulation period, or populate using linear progression or a specified value for each group (see Risk Factor Worksheets section below for full details).

The main outputs for the UKPDS Outcomes Model[®] are estimates of Life Expectancy, Quality Adjusted Life Expectancy, costs of therapies and costs of complications, all with 95% confidence intervals and with discounting applied if requested. Quality Adjusted Life Expectancy values can also be listed for each year simulated for each subject. The model also outputs cumulative event rates by simulated year, and Kaplan-Meier (KM) event-free survival.

Getting Started

OM2 is provided as a downloadable package from the DTU Secure web server. Once your license has been issued you will be provided with a time-limited username and password (see Licensing the software on page 1) in order to access the package.

If you wish, both the Macintosh and Windows packages can be downloaded. Keep the downloaded packages in a safe place should you need to re-install the software in the future, e.g. for a new computer or operating system upgrade.

Windows Platform

OM2 has been validated on the following combinations:

- Windows 7 (64bit) and Microsoft Excel 2013 (64bit)
- Windows 7 (64bit) and Microsoft Excel 2010 (64bit)
- Windows 7 (32bit) and Microsoft Excel 2013 (32bit)
- Windows 8.1 (32bit) and Microsoft Excel 2013 (32bit)

On windows the software is provided as an Installer application (UKPDS Outcomes Model Windows setup.exe). Running this application will take you step by step through the installation process.

Once completed the Outcomes Model inputs workbook can be accessed from the UKPDS Outcomes Model group on the Start menu, named UKPDS Outcomes Model v2.0 (Excel). Once opened, the workbook can be saved to any location and used as many times as required.

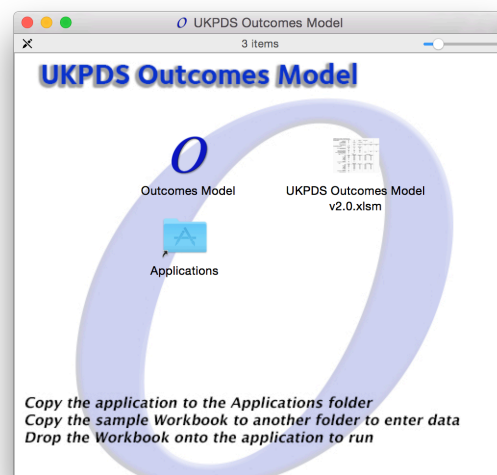
The OM2 Controller Application which runs the model can be accessed from the start menu, or the desktop icon if you choose to install one during installation.

Macintosh Platform

OM2 has been validated on the following combinations:

- Mac OS 10.9 Mavericks and Microsoft Excel 2011
- Mac OS 10.10 Yosemite and Microsoft Excel 2011

On Macintosh open UKPDS Outcomes Model.dmg by double clicking the file to open the following window:



Install the OM2 Controller Application by dragging the Outcomes Model icon to the Applications folder. The Outcomes Model Input workbook (UKPDS Outcomes Model v2.0.xlsm) file may be copied and or saved to any location and used as many times as required.

Microsoft Excel issues

Certain parts of OM2 make use of VBA macros. If macros are disabled then certain OM2 functions will not operate, including:

- Reset Costs
- Reset Utilities
- Populate annual risk factor sheets
- Verify model data

See Appendix 1 for instructions on enabling macros in Excel.

OM2 Disk Space Requirements

To process workbooks, the OM2 Controller Application needs sufficient disk space to be available on the drive that contains the users profile folder. This space is required in the temporary folder OM2 locates there, and the amount required depends upon the options selected, e.g. the number of patients, loops and bootstraps selected will make a difference.

As an example, processing a dataset with 100,000 patients for 10,000 loops and zero bootstraps would require approximately 10GB of temporary workspace. It is suggested that you ensure a sizeable amount of space is always available on the drive that contains the users profile folder.

UKPDS Outcomes Model[®] Version 2.0 (OM2) interface

OM1 used Excel Workbooks to hold the data and parameters for the model. It was also the mechanism by which the model calculations were performed, using the Run Model button on the Model Parameters worksheet. This had the advantage of being fairly simple, but limited the software to use only one CPU core. This in turn limited the speed of operation and thus lengthened the time required to complete simulations.

OM2 has changed part of this process. The model still stores its data and parameters within an Excel Workbook, but once these are populated and ready to run they are now saved and run via a Controller Application. The Controller Application enables the model to make full use of all computer cores in parallel in order to accelerate its calculations. It also permits multiple model files to be put in a queue to run sequentially unattended.

OM2 uses .xlsm files (similar to .xlsx files) rather than the .xls files used by OM1, increasing the number of patients that may be entered into a single Workbook from 65,545 to 1,048,576. The number of patient groups allowed in OM2 has been increased from 2 to 3. OM2 fully supports Mac OS X and Windows for all aspects of the model.

Controller Application Interface

Below are pictures of the Controller Application interface on Macintosh and Windows computer platforms:

Figure 1: Macintosh Controller Application interface

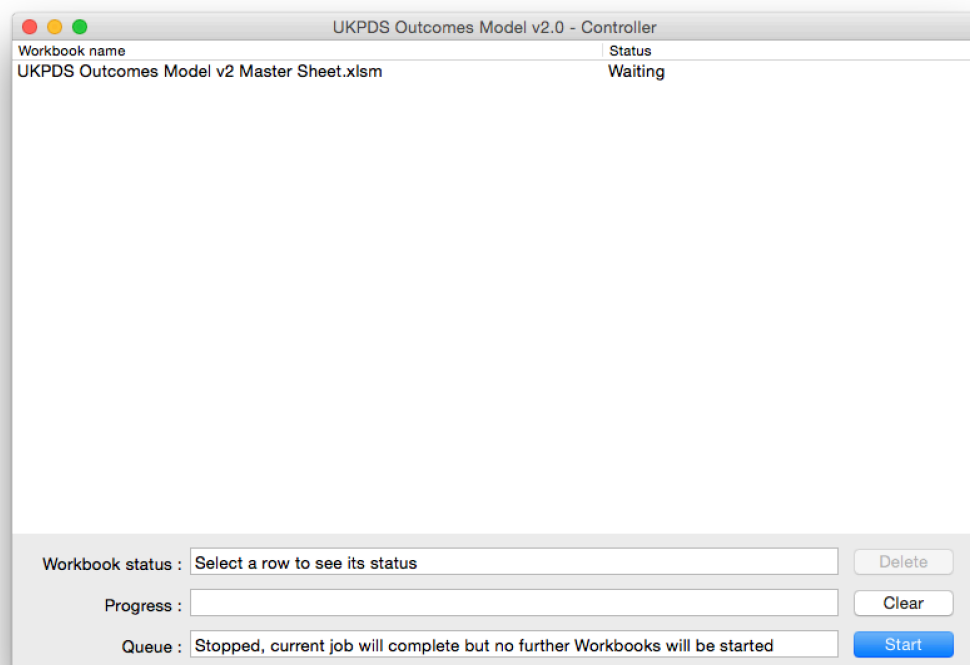
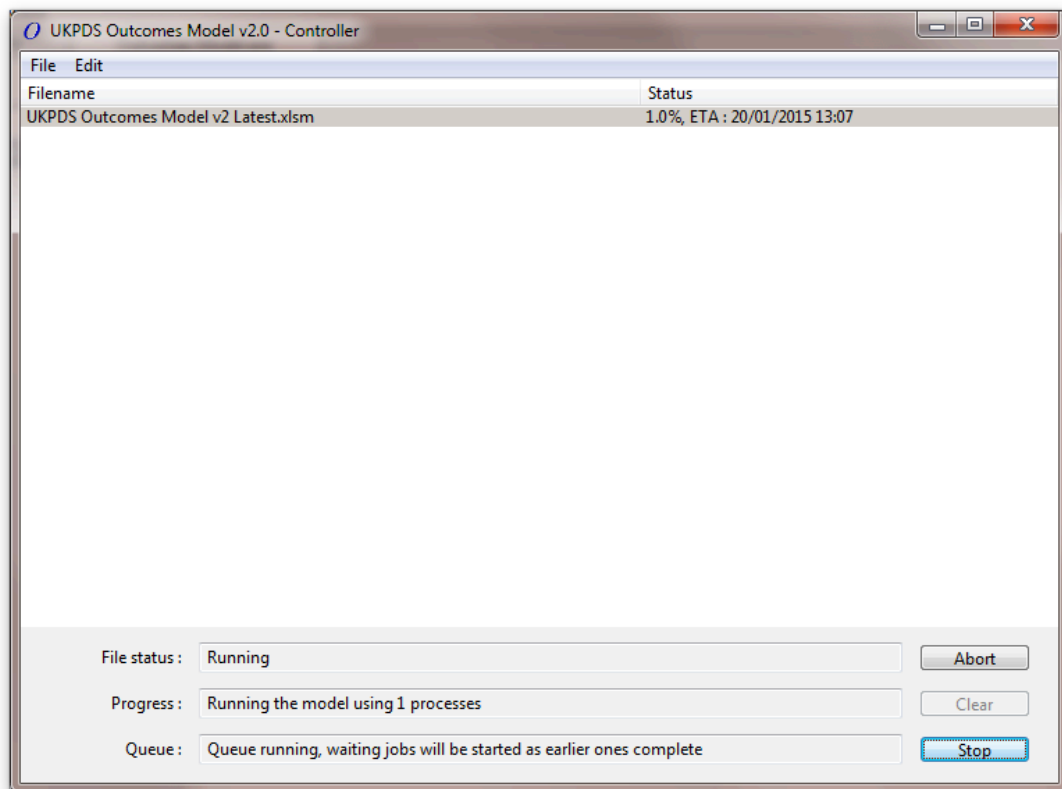


Figure 2: Windows Controller Application interface



In each case the upper area of the Controller Application interface displays the Workbook job queue, listing the Excel Workbooks that the Controller Application will process. You may add new Workbooks to the queue either by dropping them on the window or on the OM2 application icon, or by selecting them via the File Open menu. Workbooks are queued in the order they are added.

The lower part of the window displays the status panels and buttons that control the OM2 application:

Status panels

Workbook status: This shows the status of the currently selected Workbook. Select a different Workbook from the list to show its status.

Progress: Shows the current activity of the Controller Application as a whole. This panel always shows the currently active task being performed by the Controller Application, irrespective of which Workbook is selected in the list.

Queue: Shows the current state of the job queue, *i.e.* Running or Stopped.

Buttons

Start: Starts the job queue. When running, the Controller Application will process each Workbook job sequentially until it completes them all.

Stop: Stops the job queue. When stopped the Controller Application will continue to work on the currently running Workbook but when it is has been completed will not start the next one.

Clear: Allows jobs to be cleared from the list. It will ask if you wish to clear all jobs or just the completed ones. This button is only displayed when the queue is stopped and no job is active.

Delete: Allows the selected Workbook to be removed from the queue. Only displayed when the currently selected Workbook is waiting to be processed.

Abort: Allows the Workbook currently being processed to be aborted, abandoning any data produced so far. Only displayed when the currently selected Workbook is running.

Processing Workbooks and reading the results

Once one or more Workbook jobs are added to the queue you can start processing by clicking the Start button. This causes the Controller Application to process each job sequentially until all are complete, at which point the queue stops.

The results for each job are saved as a .xlsx file in the same folder as the input file, with “Outputs” appended to the filename. For example, if the input file is called “My Outcomes Workbook.xlsm” then the output file will be called “My Outcomes Workbook Outputs.xlsx”.

It is important to realise that Workbooks are only read at the time they are processed. This means that if you change a Workbook after adding it to the queue then those changes will still affect the resultant output file.

Additional jobs can be added to the queue at any time, even when the queue is running and processing data. Equally, jobs waiting to be processed can be removed from the queue before they are started.

Optimising the number of processes to use

Diabetes simulation models are complex and can take a long time to run, because each patient must be simulated multiple times and because the parameter values used to determine the transition probabilities must be varied to account for uncertainty. Simulations run times may take days, and sometimes weeks. Most modern computers have multiple processors, *i.e.* CPUs or cores, enabling simulation run times to be greatly reduced by using more than one processor. This software release of OM2 has the ability to use up to 10 CPUs.

Additional CPUs can be enabled by changing the “Number of processes to use” setting on the Model Parameters worksheet to any value from 1 to 10. It is important to select the correct number of CPUs for the machine running the model. The following guide will allow you to select the best option for your machine. Once decided, it should be the same for all models that you run on that machine. If you change your computer the number of processes should be re-optimised.

The optimisation process depends upon the type of computer you are using. Below is a guide for Microsoft Windows and another for Apple Macintosh.

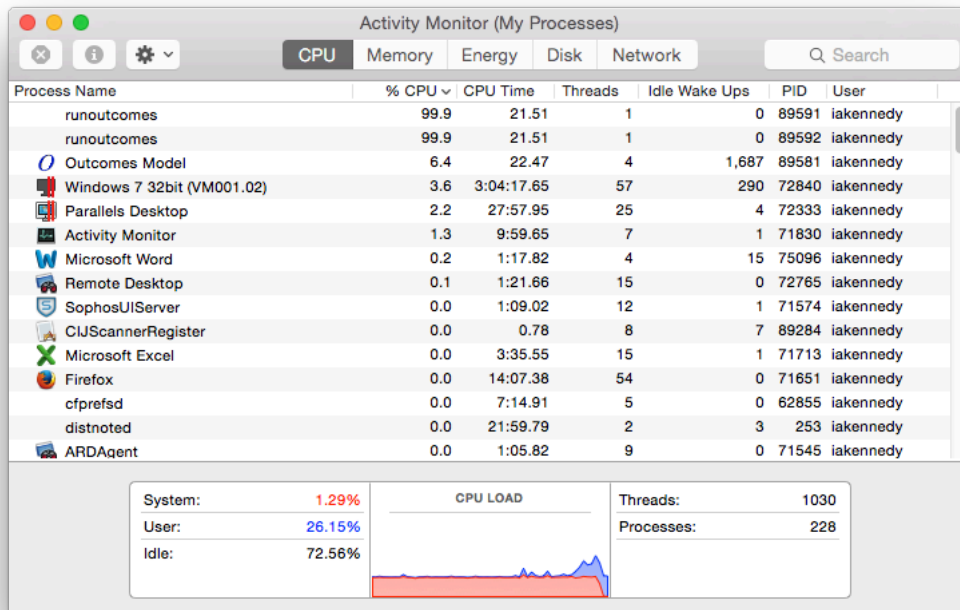
Optimising the number of processes on a Macintosh platform

On a Mac OS X machine use the Activity Monitor application provided with the operating system, which is located in the Utilities folder, as follows:

- Open Finder by clicking on its icon in the Dock.
- Select Applications on the left hand panel of the Finder window.
- Double click on the Utilities folder
- Locate the Activity Monitor application and double click to open it

Once started you should see a window similar to this:

Figure 3: Activity Monitor on a Macintosh computer



The exact window seen may differ if you are using an older version of Mac OS. To begin optimisation, ensure that the ‘CPU’ tab is selected at the top of the window and click on the ‘% CPU’ column heading in the main list. If the % CPU direction arrow points upwards, click it again so that it points downwards. You will now see a list of all the applications and processes that are running on your machine. The ‘% CPU’ column shows how much of your CPU resource each application or process is using, with the highest values at the top.

To find the best value for the number of processes you will need to do some experimentation. Take the supplied demonstration workbook and open it in the UKPDS Outcomes Model[®] Controller Application. Press the Start button while watching the results in Activity Monitor. You will see a ‘runoutcomes’ item in the process name column for every process specified on the Model Parameters page. For example, if you chose 8 processes there will be 8 rows with a Process Name of runoutcomes.

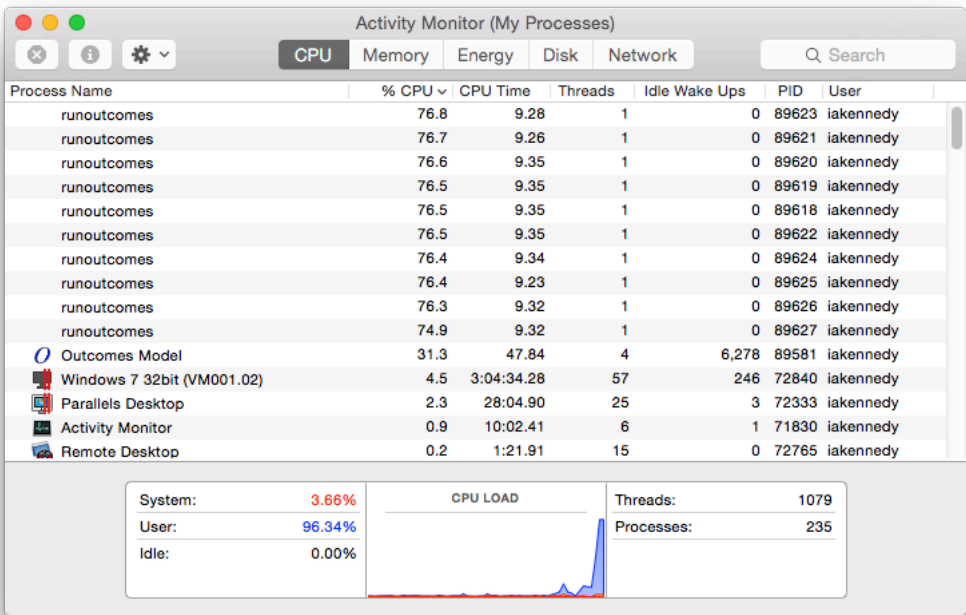
Take note of the number in the ‘% CPU’ column next to each process. Ideally these should be as close as possible to 100%. Lower values mean that too many processes are running and they are slowing each other down. Take note also of the total utilisation value, which is provided in the bottom panel and is labelled ‘user’. Once again this value should be as close to 100% as possible. Lower values mean that too

few processes are running. Once you have noted these numbers, press the Abort button in the Controller Application to stop it working.

The example shown in Figure 3 shows 2 processes called ‘runoutcomes’, each running at 99% of CPU. This is good, as it means that the processes are not fighting with each other for computer time. The overall utilization (User value), however, is only 26.15%. This is not so good as it indicates that more than 70% of the machine is idle, when it could be being used to perform your model calculations. Taken together, these values indicate that a larger number of processes can be used on this machine.

Figure 4 illustrates for the same machine running 10 processes and shows 10 rows called runoutcomes.

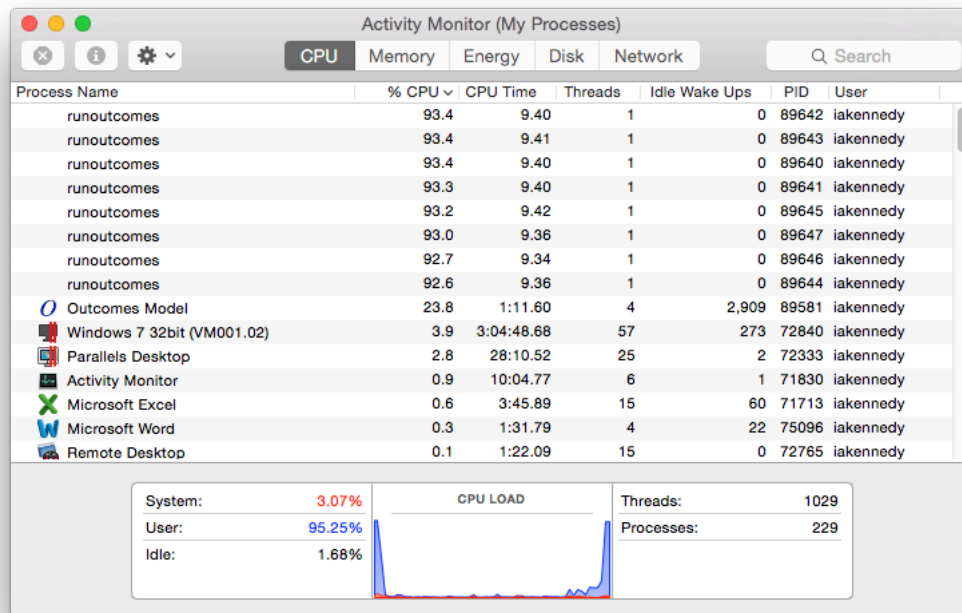
Figure 4: Activity Monitor on a Macintosh computer with 10 processes



Here the overall utilization (User value) is 96.34%, which is pretty good, as we want it to be as close to 100% as possible. This means that there are enough processes to saturate the machine. The problem, however, is that each runoutcomes process is only working at 75% capacity, indicating that the processes are fighting against each other for CPU use. Taken together these metrics show that we need to reduce the number of processes. The further away from 100% the individual values are, the more we need to reduce the number of processes.

Figure 5 shows the same machine running 8 processes.

Figure 5: Activity Monitor on a Macintosh computer with 8 processes



This time overall utilization (User value) is 95.25%, and each process is about 92.4%. With all of these values close to 100%, the number of processes has been optimised to get the fastest model performance for this machine. One word of warning though, whilst driving the machine this hard will not cause problems for the machine it will mean that you cannot do anything else with it at the same time. If you wish to use the machine for other purposes while OM2 is running, you can lower the number of processes to prevent the model software from swamping other applications.

It's also worth pointing out that working the machine this hard for an extended period of time could lead to it getting very hot. This isn't good for the hardware so the computer will start to do things to protect itself. For example it will run its fans at full speed, in an attempt to get the heat out of the computer. In extreme cases the CPU will actually slow itself down in order to run more coolly. If you are working with a very large dataset it could be worth reducing the number of processes in order to allow the computer to operate at a lower temperature.

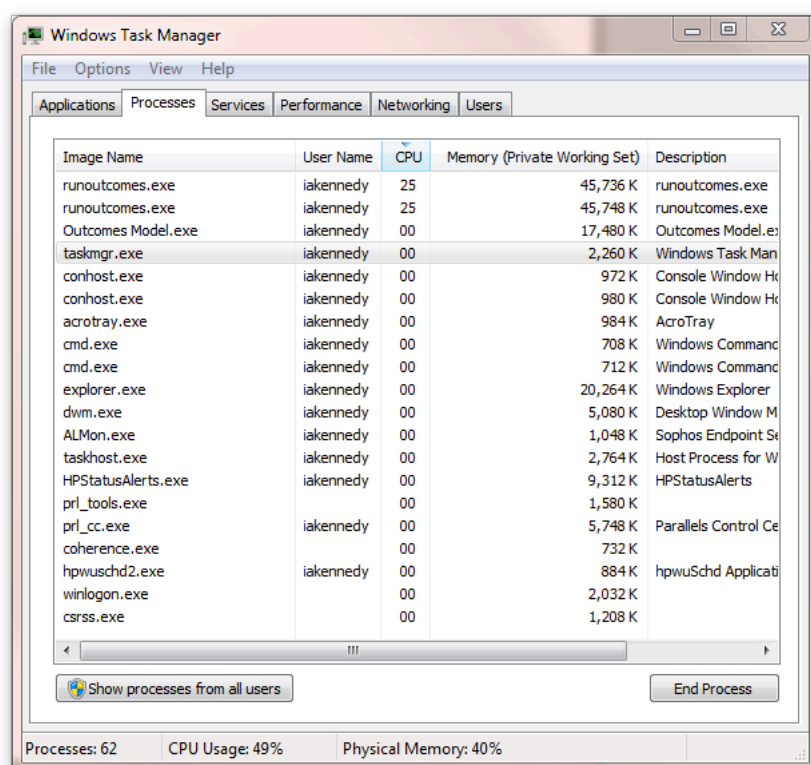
Microsoft Windows

On a Microsoft Windows machine use the Task Manager provided with the operating system. It can be started as follows:

- Right click on the Task Bar, typically at the bottom of the screen.
- Select 'Start Task Manager' from the popup menu.

Once started you should see a window similar to this: (the window may differ if you are using older versions of Windows.)

Figure 6: Activity Monitor on a Windows computer



Ensure that the 'Processes' tab is selected at the top of the window and click on the 'CPU' column heading in the main list. If the CPU arrow points upwards, click it again so that it points downwards. Once done you are now seeing a list of all the applications and processes that are running on your machine. You will now see a list of all the applications and processes that are running on your machine. The '% CPU' column shows how much of your CPU resource each application or process is using, with the highest values at the top.

To find the best value for the number of processes you will need to do some experimentation. Take the supplied demonstration workbook and open it in the UKPDS Outcomes Model[©] Controller Application. Press the Start button while watching the results in the Task Manager. You will see a 'runoutcomes.exe' item in the process name column for every process specified on the Model Parameters page. For example if you chose 8 processes there will be 8 rows whose image name is runoutcomes.exe.

The ideal value for the percentage depends upon the number of processes running. The figure is $100/\text{processes}$. For 8 processes the ideal value would be $100/8$, *i.e.* 12.5. For 2 processes it would be $100/2$ (50%), and for 4 processes it would be $100/4$ (25%).

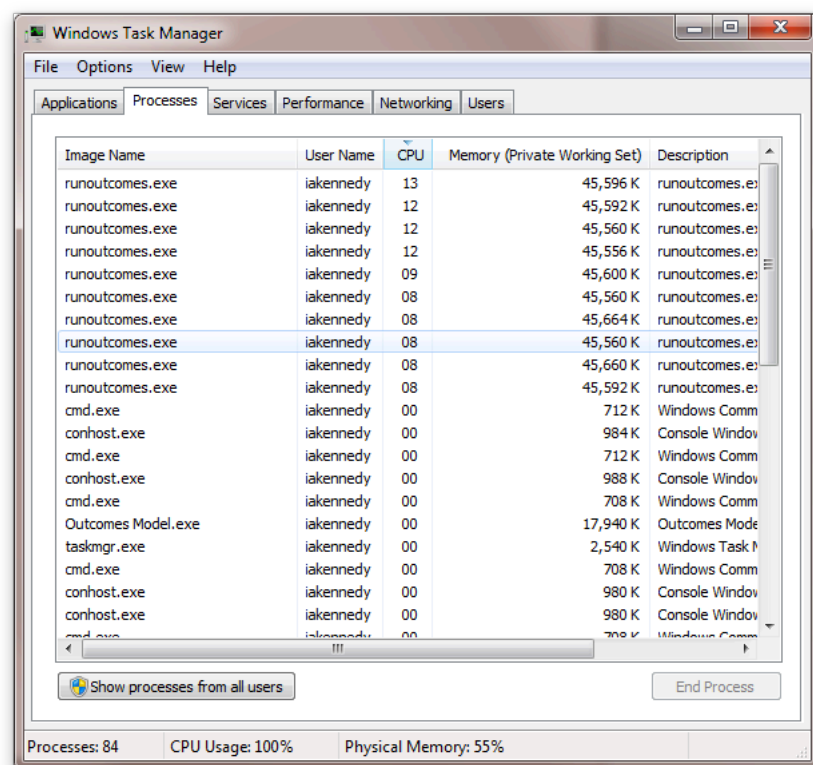
Take note of the number in the 'CPU' column next to each process. Ideally these should be as close to $100/\text{number of processes}$ as possible. Lower values mean that too many processes are running and they are slowing each other down. Take note also of the total utilisation value, which is provided in the bottom panel and is labelled 'CPU Usage'. Once again this value should be as close to 100% as possible. Lower

values mean that too few processes are running. Once you have noted these numbers, press the Abort button in the Controller Application to stop it working.

The example shown in Figure 6 shows 2 processes called 'runoutcomes.exe' with an overall utilization (CPU Usage value) of only 49%. This is not good as it indicates that more than 50% of the machine is idle, when it could be being used to perform model calculations. You can also see that each process is running at 25% of CPU. Taken together these values indicate that a larger number of processes can be used on this machine.

Figure 7 illustrates the same machine running 10 processes and shows 10 rows called runoutcomes.exe.

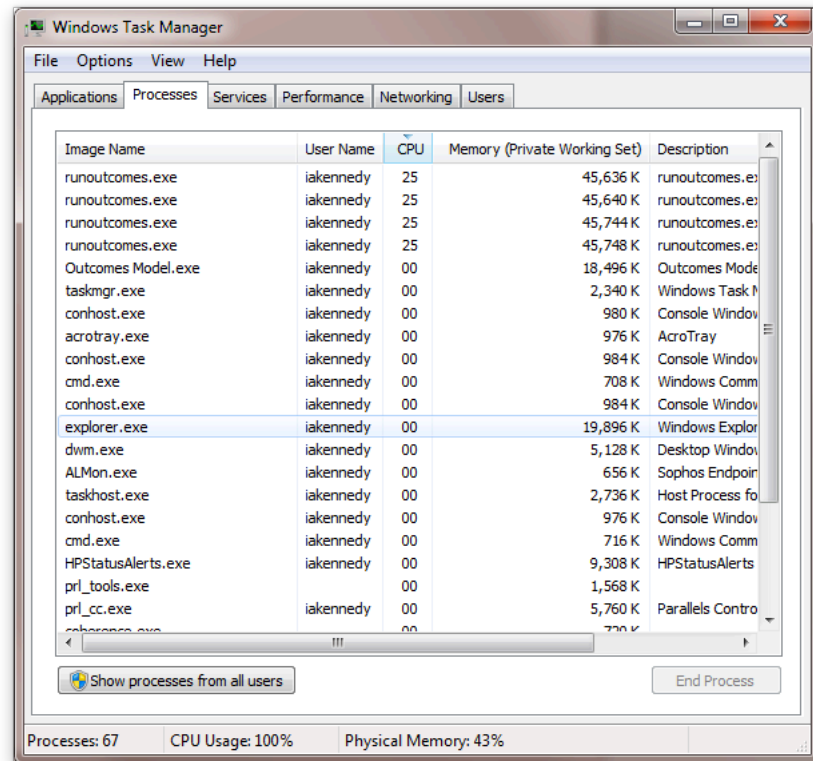
Figure 7: Activity Monitor on a Windows computer with 10 processes



Here the overall utilization (CPU Usage value) is 100%, which is excellent as we want it to be as close to 100% as possible. This means that there are enough processes to saturate the machine. Looking at the figures for each runoutcomes.exe process we can see that they vary from 8% and 13%, indicating that the processes are fighting against each other for CPU use. Taken together these metrics show that we need to reduce the number of processes.

Figure 8 shows the same machine running 4 processes.

Figure 8: Activity Monitor on a Windows computer with 4 processes



This time total utilization is 100%, and each process is showing 25%. The optimal value for each process is $100/\text{number of processes}$, so 25% ($100/4$) is perfect. With all values close to ideal, the number of processes has been optimised to get the fastest model performance for this machine.

One word of warning though, whilst driving the machine this hard will not cause problems for the machine it will mean that you cannot do anything else with it at the same time. If you wish to use the machine for other purposes while OM2 is running, you can lower the number of processes to prevent the model software from swamping other applications.

It's also worth pointing out that working the machine this hard for an extended period of time could lead to it getting very hot. This isn't good for the hardware so the computer will start to do things to protect itself. For example it will run its fans at full speed, in an attempt to get the heat out of the computer. In extreme cases the CPU will actually slow itself down in order to run more coolly. If you are working with a very large dataset it could be worth reducing the number of processes in order to allow the computer to operate at a lower temperature.

Description of the Workbooks used by the model

The UKPDS Outcomes Model[®] software is run as described above using the Controller Application Interface, but the main data input and output is conducted via Microsoft Excel[™] workbooks. This provides users with a straightforward method for entering or importing details of populations to be simulated, viewing results, and printing or exporting them easily to other software packages.

The Input Workbook contains a series of worksheets that hold the various model inputs and the parameters used when running the calculations. It provides methods for populating missing data and for verifying data prior to submission to the Controller Application.

The Controller Application produces an Output Workbook for each Input Workbook processed. The data from the Input Workbook is reproduced along with the various model outputs. The Output Workbook, produced as a .xlsx file, is placed in the same folder as the Input Workbook with “Outputs” appended to its filename. For example, if the Input Workbook is called ‘My Outcomes Data.xlsm’ then the Output Workbook will be called ‘My Outcomes Data Outputs.xlsm’.

A more detailed description of the worksheets found in each type of workbook and their uses is given below.

N.B. It is essential that:

- Worksheets contained within the workbooks are not rearranged in any way.
- Columns within the worksheets are not reordered.

The Input Workbook

The Input Workbook is a .xlsm file. This file type is required to allow the embedded macros to function and to still maintain the maximum number of available rows. Do not save the workbook in any other format (including .xls format), as it could result in data loss, prevent the macros from working correctly and prevent it from being recognised by the Controller Application.

All values in the Inputs Workbook must be provided prior to running the model. Methods are provided in the Risk Factor worksheets on how to populate the values on these worksheets in a variety of ways. This feature replaces the equations built in to the OM1 software that internally predicted missing values. Moving this functionality into the Inputs Workbook enables improved control of the values used and provides greater clarity with respect to the values used by the model in a given year.

The Input Workbook has the following worksheets:

About Worksheet

This contains a brief description of UKPDS Outcomes Model[®] Version 2.

Inputs Worksheet

This Inputs Worksheet is used to enter patient baseline characteristics, risk factor values and history of previous events, with a single row for each subject. A subject ID

can be specified in column A. The following changes have been made in OM2, compared with OM1:

- Age has been changed from age at diagnosis to Age now
- Smoking status is now specified as yes/no.
- Total cholesterol has been replaced with LDL-cholesterol, alongside the pre-existing HDL-cholesterol.
- Albuminuria, Heart rate, WBC, Haemoglobin and eGFR have been added.
- Ulcer has been added to the pre-existing events section.
- Values at Diagnosis are no longer required.

All values in the Inputs Worksheet are mandatory, with the exception of Years since prior event. A blank cell in these columns indicates that the event has never taken place, a 0 forces the event to occur in the first year of simulation, and a 1 (or any other value) indicates that the event took place prior to the start of simulation. True time since a prior event occurred may be entered, but the model only discriminates between no event, event in the first year of simulation, and event prior to the start of simulation.

The Discounting start year parameter is used to set the offset year for discounting in the first year of simulation on a *per* subject basis, *e.g.* entering 10 instructs the model to apply a discounting year of 10 in the year 1 outputs from the simulation.

A Subject ID is required but it is not necessary for it to be unique.

Figure 9: Inputs Worksheet

	A	B	C	D	E	F	G	H	I
1	UKPDS Outcomes Model : Inputs								
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)								
3									
4									
5									
6									
7									
8	Subject Characteristics								
9	Demographic characteristics								
10	ID	Group	Ethnicity	Gender	Age now	Duration of diabetes	Weight	Height	AF
11									
12									
13									
14									
15									
16		1, 2 or 3	1 = White, 2 = Afro-Caribbean, 3 = Asian-Indian	M=Male, F=Female	(y)	(y)	(kg)	(m)	N=Not present, Y=Present
17	001A	1	1	M	60	10	50	1.8	N
18	002B	1	1	M	60	10	55	1.8	Y
19	003C	1	3	M	60	10	60	1.8	N
20	004D	1	3	M	60	10	65	1.8	Y

Figure 9: Inputs Worksheet (contd.)

[illegible]

Risk Factor Worksheets

There are 13 risk factor worksheets, with yellow tabs: smoking status, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, peripheral vascular disease, atrial fibrillation, weight, albuminuria, heart rate, white blood cell count, haemoglobin and eGFR.

Each of these worksheets allows the user to specify values for each risk factor on a year-by-year basis. Users may paste in their own data or use one of the built in methods for populating the values. In either case a value must be provided for each year being simulated.

For continuous risk factors (HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, weight, heart rate, white blood cell count, haemoglobin and eGFR), two methods for populating the worksheet are provided:

- 1) Copy the value from the Inputs worksheet into every year, effectively holding the initial values constant for the simulation period.

- 2) Populate using linear regression ($y=mx+c$), where y is the result for a given year and x is the value from the prior year, or the initial value from the inputs worksheet for the first year. Values for m and c can be specified by group)

Figure 10: Typical continuous risk factor worksheet

	A	B	C	D	E	F	G	H	I	J
1	UKPDS Outcomes Model : Updated HDL cholesterol (mmol/l) by simulated year									
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)									
3										
4	Populate sheet									
5	Method :	2	(1 = Match subjects initial value, 2 = $y=mx + c$)							
6	Replace existing :	Y	(Y = Overwrite current values in this sheet, N = Preserve the current value of cells, populating only empty ones)							
7	Group :	1	2	3						
8	m :	1.01	1.02	1.03						
9	c :	0.00	0.00	0.00						
10										
11	For Year 1 x is the initial value from the Inputs sheet									
12	For subsequent years x is the prior year									
13	Data will be populated for the number of patients specified in the Model Parameters sheet (cell C4) and the number of years (cell C7)									
14										
15										
16	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
17	1	1.3265298	1.2787782	1.2503175	1.2333952	1.2233796	1.2174963	1.2140819	1.2121393	1.2110712
18	2	1.890526	1.7695442	1.6968872	1.6532913	1.6271774	1.6115782	1.6023001	1.5968187	1.5936147
19	3	1.199083	1.136376	1.0988894	1.0765198	1.0632166	1.055349	1.0507371	1.0480719	1.0465675
20	4	1.5086763	1.4372744	1.3945402	1.3690035	1.3537889	1.3447677	1.3394596	1.3363742	1.3346162

◀◀◀▶▶▶

About

Inputs

Smoking Status

HDL

LDL

Systolic BP

HbA1c

Normal View

Ready

For binary risk factors (smoking status, peripheral vascular disease, atrial fibrillation, albuminuria), two methods of populating the worksheet are provided:

- 1) Copy the value from the Inputs worksheet into every year, effectively holding the initial values constant for the simulation period.
- 2) Populate each year with a specified value for each group.

Figure 11: Typical binary risk factor worksheet

	A	B	C	D	E	F	G	H	I	J						
1	UKPDS Outcomes Model : Updated smoking status (Y=Current smoker of tobacco, N=N															
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)															
3																
4	Populate sheet															
5	Method :	2	(1 = Match subjects initial value, 2 = Set values for groups from value below)													
6	Replace existing :	Y	(Y = Overwrite current values in this sheet, N = Preserve the current value of cells, populating only empty ones)													
7	Group :	1	2	3												
8	Value :	N	Y	Y												
9																
10																
11																
12																
13	Data will be populated for the number of patients specified in the Model Parameters sheet (cell C4) and the number of years (cell C7)															
14																
15																
16	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9						
17	1	Y	Y	Y	N	N	N	N	N	N						
18	2	N	N	N	N	N	N	N	N	N						
19	3	N	N	N	N	Y	Y	Y	Y	Y						
20	4	N	N	N	N	N	N	N	N	N						

</

Users should specify on each worksheet whether they wish their selected method to overwrite all cells on that worksheet, including those where values are already present, or to preserve current values on the worksheet and only populate empty cells.

Once all 13 worksheets are configured they can be populated by visiting the Model Parameters worksheet, selecting the subjects and number of years to operate on and then clicking the 'Populate annual risk factor worksheets' button.

The subject ID column in each Risk Factor worksheet is required to match that provided on the Inputs Worksheet for the same row number.

Smoking Status Worksheet

This worksheet is used to enter the smoking status by subject for each of the years to be simulated: Y=current tobacco smoker, N=non-smoker or ex-smoker.

HDL Worksheet

Use this worksheet to enter HDL-cholesterol values (mmol/l) by subject for each year to be simulated. Ideally these should be from a CDC (Centre for Disease Control) aligned assay.

LDL Worksheet

Use this worksheet to enter LDL-cholesterol values (mmol/l) by subject for each year to be simulated. Ideally these should be from a CDC aligned assay. This is a new worksheet in OM2.

Systolic BP Worksheet

Use this worksheet to enter systolic blood pressure values (mmHg) by subject for each year to be simulated.

HbA_{1c} Worksheet

Use this worksheet to enter HbA_{1c} values (%) by subject for each of the years to be simulated. Ideally these should be from a DCCT (Diabetes Control and Complications Trial) or NGSP (National Glycohemoglobin Standardization Programme) aligned assay.

PVD Worksheet

Use this worksheet to enter peripheral vascular disease status by subject for each year to be simulated: Y = present, N = not present.

AF Worksheet

Use this worksheet to enter atrial fibrillation status by subject for each year to be simulated: Y = present, N = not present.

Weight Worksheet

Use this worksheet to enter body weight values (kg) by subject for each year to be simulated. If only the BMI (body mass index) is available, then entering that in the Weight Worksheet and setting the Height to 1 is acceptable. This is a new worksheet in OM2.

Albuminuria Worksheet

Use this worksheet to enter albuminuria status by subject for each year to be simulated: Y = micro or macroalbuminuria, N = None. This is a new worksheet in OM2.

Heart rate Worksheet

Use this worksheet to enter heart rate values (bpm) by subject for each year to be simulated. This is a new worksheet in OM2.

WBC Worksheet

Use this worksheet to enter white blood cell count values ($\times 10^9$ per litre) by subject for each year to be simulated. This is a new worksheet in OM2.

Haemoglobin Worksheet

Use this worksheet to enter haemoglobin values (g/dl) by subject for each year to be simulated. This is a new worksheet in OM2.

eGFR Worksheet

Use this worksheet to enter eGFR values (ml/min/1.73m²) by subject for each year to be simulated. This is a new worksheet in OM2.

Model parameters Worksheet

Use this worksheet (Figure 12) to configure a set of model parameter values. These include:

Subject rows

Specifies the first and last subject row to be included in the simulation. (The available rows and number of subjects selected is displayed alongside the entries). This is a change from OM1 which always starts with the first subject.

Number of loops

Sets the number of internal loops (Monte-Carlo trials) *per* subject to reduce first order uncertainty (Monte Carlo Error - MCE). OM1 and OM2 are micro-simulation models that use Monte Carlo methods to simulate identical patients one at a time through the model several times while recording the outcome(s) of each loop (Monte-Carlo trial), x_i . The *per*-patient outcome(s) are calculated by dividing the total simulated number of events (e.g. myocardial infarction) by the total number of n loops, \bar{X}_n .

Due to the random nature of Monte Carlo, the predicted outcome(s) for each subject varies with each internal loop. This random noise is called MCE and will be reduced considerably if a sufficient number of loops (Monte-Carlo trials) are performed.

The MCE for a given outcome is estimated as the standard deviation of the outcome across the number on Monte-Carlo trials, SD_n , divided by the squared root of number of trials,

$$SD_n = \sqrt{\frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{X}_n)^2}$$

$$MCE_n = \frac{SD_n}{\sqrt{n}}$$

For $i=1, \dots, n$ loops/trials

Performing more loops (n) produces more stable predicted outcomes for each subject, i.e. reduces MCE, but takes longer. The relative error for each outcome can also be estimated by dividing the MCE by the predicted mean. A rule of thumb is to achieve a relative error <1-5% of the statistic of interest for each outcome (e.g. mean life expectancy, standard deviation of life expectancy, etc.).

Past experimentation suggests 5,000 or more loops are required to obtain stable estimates at patient level, but when looking at aggregate outcomes for a cohort a minimum of 1,000 loops may be appropriate. The user should be aware that the optimal number of inner loops depends on: 1) frequency/size of the simulated event of interest (e.g. life expectancy, stroke rates, costs, etc.); 2) whether accurate estimates are wanted at patient or cohort level and; 3) whether the focus is on estimating differences between groups or obtaining accurate estimates of the outcome(s) at group level. For example, to obtain precise estimates of the difference in life expectancy between two groups, the number of loops required is inversely related with the expected size of the difference. Hence, users should experiment with different numbers of loops to test stability, i.e. that the results of interest do not vary significantly between simulations.

Figure12: Model Parameters Worksheet

	A	B	C	D	E	F	G
1	UKPDS Outcomes Model : Model Parameters						
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)						
3	Processing options						
4		First	Last	Available rows	Number of subjects		
5		Subject rows :	17	400	384		
6		Number of loops :	100	(1+)			
7		Number of bootstraps :	100	(0 to 5000, ≠1)	Start bootstrap :	1	(1 to 5000)
8		Number of years simulated :	70	(1 to 70)			
9		Number of processes to use :	2	(1 to 10)	(Each process you run works on a subset of the data in parallel speeding up execution. You should set this to the number of processors on your machine.)		
10			Process 1	Process 2	Process 3	Process 4	Process 5
11		Random number seed :	(1 to 100)	1	2	3	4
12	Cost and utility parameters						
13		Initial rate	for n years	Subsequent rate			
14		(0 to 100%)	(0 - 70)	(0 to 100%)			
15		QALE/Life expectancy discount rate :	3.5%	10	3.0%		
16		Total costs discount rate :	3.5%	10	3.0%		
17							
18		Group 1	Group 2	Group 3			
19		Therapy cost prior to complication :	500.00	750.00	1,000.00		
20		Number of years to apply from start :	2	5	10		
21		Therapy cost post complication :	500.00	750.00	1,000.00		
22		Number of years to apply from complication :	70	70	70		
23							
24		Use these costs/utilities until age :	50	(0 to 200)			
25		Male					
26			At time of event		In subsequent years		
27			Fatal cost	Non-fatal cost	Cost	Utility decrement	
28		IHD :	4,153.00	9,583.00	0.000	1,423.00	0.000
29		MI :	2,062.00	6,775.00	-0.065	1,397.00	0.000
30		Heart failure :	0.00	3,550.00	-0.101	1,935.00	-0.101
31		Stroke :	4,629.00	6,614.00	-0.165	1,461.00	-0.165
32		Amputation :	0.00	11,480.00	-0.172	2,827.00	-0.172
33		Blindness :	0.00	2,665.00	0.000	967.00	0.000
34		Renal failure :	0.00	30,000.00	-0.200	30,000.00	-0.200
35		Ulcer :	0.00	5,000.00	-0.050	1,000.00	-0.050
36							
37		Initial utility :	0.807	(0 to 1)			
38		Cost in the absence of complications :	771.00				
39							
40		Female					
41			Fatal cost	Non-fatal cost	Cost	Utility decrement	
42		IHD :	4,546.00	10,135.00	0.000	1,710.00	0.000
43		MI :	7,464.00	12,218.00	-0.065	1,682.00	0.000
44		Heart failure :	0.00	3,959.00	-0.101	2,244.00	-0.101
45		Stroke :	5,010.00	7,183.00	-0.165	1,737.00	-0.165
46		Amputation :	0.00	11,958.00	-0.172	3,166.00	-0.172
47		Blindness :	0.00	2,966.00	0.000	1,191.00	0.000
48		Renal failure :	0.00	30,000.00	-0.200	30,000.00	-0.200
49		Ulcer :	0.00	5,000.00	-0.050	1,000.00	-0.050
50							
51		Initial utility :	0.807	(0 to 1)			
52		Cost in the absence of complications :	991.00				
53							
54		Currency conversion value :	1.00				
55							
56							
57							
58							
59							
60							
61							
62							
63		Status :	Validation complete - 0 error(s) found				
64		Workbook version :	2.0				
65		Workbook release date :	09 Mar 2015				
66		Last validated :	24 Mar 2015 16:45:49				
67		Time taken :	00:00:16				
68							

Reset Costs

Reset Utilities

Populate annual risk factor sheets

Populate annual risk factor sheet. Data already on th

Validate Model

Validate model will check Validation worksheet. A r

Number of bootstraps

Sets the number of bootstraps to address second order uncertainty and thus to estimate confidence intervals around Life Expectancy, Quality Adjusted Life Expectancy, therapy and complication costs. The OM2 software contains 5,000 full sets of model equation parameters derived from bootstrap samples of the UKPDS trial population, which were generated by sampling with replacement from the original data set. This is an increase from the 999 bootstraps provided in OM1. When the desired number of bootstraps has been chosen, each bootstrap run will use a different set of model equation parameters from those available. Larger numbers internal loops and bootstraps will give more precise confidence intervals, and users should experiment to assess the number required in their particular simulations to obtain stable confidence intervals. A very important first step is to minimise MCE by finding the optimal number of inner loops and then test the number of bootstraps. If the number of bootstraps is set to 0 then no confidence intervals will be generated and the model will run with the equations as published. A value of 1 for the Number of bootstraps will be rejected as calculation of confidence intervals requires at least two bootstraps.

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Start at bootstrap

Sets which of the 5000 bootstrap parameters sets supplied in OM2 should be used first. Parameter sets are used sequentially, with wrap round to the first set if necessary.

Number of years simulated

Sets the maximum possible number of years to be simulated *per* subject. The time taken to run the model can be reduced by not specifying more years to be simulated than necessary. The current version of OM2 is limited to a maximum of 70 years, an increase from the 40-year limit in OM1. No minimum age is specified for patients, but users should bear in mind that UKPDs participants, although recruited with new-onset type 2 diabetes over the age range 25-65 inclusive, had a median age of 53 years.

Number of processes

Sets the maximum number of processes that will be used to process the dataset. Each process takes a subset of the data and works on it separately. Performing model calculations in parallel can significantly reduce the time taken to run the model. A different random number seed can be selected for each process. Further details and optimisation advice are given above in the Controller Application Interface section above.

Discount rates

Sets the annual discount rate to be applied to estimates of Life Expectancy, Quality Adjusted Life Expectancy and therapy and complication costs. Two different discount rates can be applied for one simulation, *e.g.* a discount rate of 3% can be specified for the first 10 years and then 1.5% for all subsequent years. If discounting is not required enter “0” for the discount rate. Separate discount rates can be applied for costs and life expectancy.

Therapy costs

Sets the therapy costs to be applied to each group, the number of years from the start of simulation in which they apply, whether they change post-complication and, if so, which events trigger the post-complication therapy costs and the number of years they apply following the complication(s). This is a new feature in OM2.

Use these costs/utilities until age

Defines the age limits for each of up to five age blocks. Scroll to the right to see the additional blocks. The cost/utility values within the block are used up until the subject reaches a simulated age above this value. Separate costs and utilities are provided for each gender within each block.

If you do not wish to use a given block then clearing the age limit for that block will cause it to be ignored. For example, to use a single set of costs and utility values for subjects independent of age set the age limit of the first block to 200 and clear the

value for the other blocks. OM1 only supported one block of costs and they were not split by gender.

Initial Utility value

This sets the initial quality of life value at the start of the simulation from which decrements are subtracted when calculating QALYs. Initial utility levels can be set for each age block, but not at the individual patient level. The value of Age now for the subject is used to select which of the blocks apply for that subject. The default value of 0.807 is derived from UKPDS patients without complications and published in 2014.⁴

Cost in absence of complications

Sets the annual cost incurred by a subject in the absence of any of the complications simulated in OM2. The value applied for a given year of simulation is based upon their age in that year. Age- and gender-specific default values are provided, based on updated estimates derived from UKPDS patients and published in 2015.⁵

Utility Decrements

Sets utility decrements associated with IHD, MI, heart failure, stroke, amputation, blindness, renal failure and ulcer by age in the year of simulation.

Default values are provided, based on updated estimates derived from UKPDS patients and published in 2014.⁴ The defaults provided for renal failure and for ulcer are taken from a meta-analysis of quality of life studies,⁶ and are not UKPDS-based. They have simply been provided for convenience and it should not be inferred that these are the “best” estimates available. They are shown in the worksheet in italics. Users may select their own age- and gender-specific values for the initial and subsequent utility decrement associated with each of these events.

Complication costs

Sets the complication costs associated with IHD, MI, heart failure, stroke, amputation, blindness, renal failure and ulcer. These include costs incurred in the year of the complication, and costs incurred in subsequent years.

Age- and gender-specific default values are provided, based on updated estimates derived from UKPDS patients and published in 2015.⁵ The defaults provided for costs associated with renal failure and ulcer are taken from the NHS Blood and Transplant programme⁷ and a recent UK report on the costs of ulcer and amputation⁸ respectively, and are not UKPDS-based. The renal failure default cost of £19,190 per year in the year of event and in subsequent years assumes that 45% of patients are transplanted and 55% are on dialysis, that 24% of those on dialysis are on peritoneal and 76% on haemodialysis, and that costs are £17,500 per patient per year for a patient on peritoneal dialysis, £35,000 per patient per year for a patient on hospital haemodialysis, and £5000 per year following transplantation.⁷ The costs of an ulcer, of £6599 in the year of the event only, assume community costs of £4992, in-patient costs of £3215, 50% of patients admitted as in-patients and all patients receiving community care.⁸ These have simply been provided for convenience and it should not be inferred that these are the “best” estimates available. They are shown in the

worksheet in italics. Users may select their own values for the initial and subsequent complication costs associated with each of these events.

Currency Conversion Value

The exchange rate value applied to the default costs when the Reset costs button is used. This is a new feature in OM2.

Reset Costs button

Click this button to revert to default Costs as supplied with this version of OM2. The values provided are multiplied by the Currency Conversion Value.

Reset Utilities button

Click this button to revert to the default utility decrements as supplied with this version of OM2.

Populate annual risk factor worksheet button

Used to populate the 13 Risk Factor worksheets (smoking status, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, peripheral vascular disease, atrial fibrillation, weight, albuminuria, heart rate, white blood cell count, haemoglobin and eGFR) using the methods selected on the individual worksheet. Note that this must be done when there are blank cells in any of the risk factor worksheets before attempting to run the model or errors will occur. Values are calculated for the subjects selected in the Subject Rows parameters described above and for the Number of years specified. Data outside of this range will remain unchanged.

For more details of the methods available for each worksheet see Risk Factor section above. This is a new feature in OM2.

Verify Model Data button

Checks the Input Worksheets for errors. Checks include: missing data, out of range values, or invalid values for the Inputs worksheet, all Risk Factor worksheets and the model parameters worksheet. Any anomalies are marked in red. Issues are summarised on the Errors worksheet. This is equivalent to the Pre-flight check option in OM1.

Clicking on button also updates the Inputs Check worksheet (see below).

Inputs Check Worksheet (Figure 13)

This worksheet provides the means and standard deviation (SD) or counts by column for Inputs Worksheet data, by group and for all patients. It also provides the counts (binary data) or mean and SD (continuous data) for all Risk Factor worksheets, by group, and for all patients, and by year of simulation. These data are updated whenever the Verify Model Data button is clicked.

Figure 13: Inputs check worksheet

	A	B	C	D	E	F	G	H
1	UKPDS	Outcomes Model : Inputs Checks						
2	Version 2.0	© Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)						
3	Subject	Characteristics						
4			Demographic characteristics					
5			Ethnicity	Gender	Age now	Duration of diabetes	Weight	Height
6	All	Count	(0,1,2)	(M,F)	(y)	(y)	(kg)	(m)
7		0	0	0	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)
8		0	0	0	0	0	0	0
9		0	0	0	0	0	0	0
10	Group 1							
11		0	0	0	0	0	0	0
12		0	0	0	0	0	0	0
13		0	0	0	0	0	0	0
14	Group 2							
15		0	0	0	0	0	0	0
16		0	0	0	0	0	0	0
17		0	0	0	0	0	0	0
18	Group 3							
19		0	0	0	0	0	0	0
20		0	0	0	0	0	0	0
21		0	0	0	0	0	0	0

	A	I	J	K	L	M	N	O	P
1	UKPDS								
2	Version 2.0								
3	Subject								
4			Current risk factor values						
5		AF	PVD	Smoking	Albuminuria	HDL	LDL	Systolic BP	HbA1c
6	All	(Y,N)	(Y,N)	(Y,N)	(Y,N)	(mmol/l)	(mmol/l)	(mmHg)	(%)
7		0	0	0	0	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)
8		0	0	0	0	0	0	0	0
9		0	0	0	0	0	0	0	0
10	Group 1								
11		0	0	0	0	0	0	0	0
12		0	0	0	0	0	0	0	0
13		0	0	0	0	0	0	0	0
14	Group 2								
15		0	0	0	0	0	0	0	0
16		0	0	0	0	0	0	0	0
17		0	0	0	0	0	0	0	0
18	Group 3								
19		0	0	0	0	0	0	0	0
20		0	0	0	0	0	0	0	0
21		0	0	0	0	0	0	0	0

	A	X	Y	Z	AA	AB	AC	AD	AE	AF
1	UKPDS									
2	Version 2.0									
3	Subject									
4		Years since pre-existing event								
5		Blindness	Renal failure	Stroke	MI	Ulcer	Discounting start			
6	All	(y)	(y)	(y)	(y)	(y)	year			
7		(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)			
8		0	0	0	0	0	0			
9		0	0	0	0	0	0			
10	Group 1									
11		0	0	0	0	0	0			
12		0	0	0	0	0	0			
13		0	0	0	0	0	0			
14	Group 2									
15		0	0	0	0	0	0			
16		0	0	0	0	0	0			
17		0	0	0	0	0	0			
18	Group 3									
19		0	0	0	0	0	0			
20		0	0	0	0	0	0			
21		0	0	0	0	0	0			

	A	P	Q	R	S	T	U	V	W
1	UKPDS								
2	Version 2.0								
3	Subject								
4									
5		HbA1c	Heart rate	WBC	Haemoglobin	eGFR	IHD	Heart failure	Amputation
6	All	(%)	(bpm)	(x10 ⁹ /l)	(g/dl)	(ml/min/1.73m ²)	(y)	(y)	(y)
7		(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)	(Mean,SD,N)
8		0	0	0	0	0	0	0	0
9		0	0	0	0	0	0	0	0
10	Group 1								
11		0	0	0	0	0	0	0	0
12		0	0	0	0	0	0	0	0
13		0	0	0	0	0	0	0	0
14	Group 2								
15		0	0	0	0	0	0	0	0
16		0	0	0	0	0	0	0	0
17		0	0	0	0	0	0	0	0
18	Group 3								
19		0	0	0	0	0	0	0	0
20		0	0	0	0	0	0	0	0
21		0	0	0	0	0	0	0	0

Errors

Any errors that are found by the Verify Model Data button are displayed in the Errors worksheet. The top section summarises issues with the Model Parameters worksheet and a row for each subject summarises any issues found on the Inputs or Risk Factor worksheets. This is a new feature in OM2.

The Output Workbook

The Output Workbook reproduces the worksheets found in the Input Workbook (apart from the Errors worksheet), and adds additional worksheets to provide the outputs from the model. The Estimated risk factors worksheets found in version 1 of the model have been removed from this version, as the data used by the model is fully visible within the Risk Factor worksheets. The following additional worksheets are provided:

Outputs Worksheet

This worksheet (Figure 14) tabulates Life Expectancy, Quality Adjusted Life Expectancy, cumulative therapy costs, cumulative complication costs, and cumulative total costs together with their respective 95% confidence intervals, for each subject specified. The worksheet also includes Expected utility, therapy costs, complication costs, total costs by simulated year.

Overall values for the population are provided, as well as summary data for each group, and the group differences (1 vs. 2, 1 vs. 3, 2 vs. 3). Monte Carlo error (MCE) (see 'Number of loops') is also calculated for the overall population, for each group and for their differences, but not for the individual subject data.

Figure 14: Outputs worksheet

	A	B	C	D	E	F	G	H	I
1	UKPDS Outcomes Model : Outputs								
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)								
3			MCE	95% CI			MCE	95% CI	
4	ID	Life expectancy		Lower	Upper	Total QALE		Lower	Upper
5	All:	3.410205431	0.0227634	3.0436203	4.1979491	0.718800324	0.0211792	-0.440497	0.9245357
6	Group 1:	3.319547335	0.035334	2.9337085	4.0783462	0.691305264	0.0323188	-0.399958	0.8984719
7	Group 2:	3.475302922	0.0369465	3.0884331	4.2458543	0.720894463	0.0348239	-0.454079	0.9464998
8	Group 3:	3.455374892	0.0499226	3.1339586	4.327935	0.765214348	0.0466298	-0.489481	0.9863313
9	Difference 1,2:	-0.155755587	0.0389395	-0.249188	-0.069155	-0.029589199	0.0399472	-0.111539	0.0894857
10	Difference 1,3:	-0.135827557	0.0466335	-0.33825	-0.083939	-0.073909085	0.0438782	-0.162713	0.1032287
11	Difference 2,3:	0.019928029	0.0486775	-0.123763	0.0496658	-0.044319886	0.0421278	-0.1601	0.0718801
12									
13									
14									
15									
16									
17	001A	3.842810378	-	1.189978	7.347421	0.511544002	-	-4.606612	0.915339
18	002B	1.622485363	-	0.679993	2.750371	0.139773452	-	-1.694261	0.33492
19	003C	5.987893298	-	4.567542	7.105449	4.789878858	-	3.499884	5.536739
20	004D	3.63791018	-	2.894341	4.977422	-0.012845664	-	-2.341429	0.452843

	A	J	K	L	M	N	O	P	Q
1	UKPDS Outcomes								
2	Version 2.0 © Isis Inn								
3									
4	ID	Therapy costs	MCE	95% CI		Cost of complications	MCE	95% CI	
5	All:	1378.760989	10.108238	1285.2249	1633.939	52356.71077	500.13327	45959.892	62863.261
6	Group 1:	512.7642814	3.9697906	487.27428	636.21893	52229.19632	790.10317	45481.829	62680.151
7	Group 2:	1462.685386	12.237557	1366.8798	1685.7605	53292.23045	813.76554	46588.844	63103.951
8	Group 3:	2807.334133	35.434843	2595.9256	3366.7518	50855.83487	1058.5713	46036.688	61980.286
9	Difference 1,2:	-949.9211047	7.164491	-1087.186	-883.8486	-1063.034127	670.7043	-3204.788	885.33412
10	Difference 1,3:	-2294.569851	23.178738	-2752.712	-2155.457	1373.361448	816.3563	-1892.633	2127.542
11	Difference 2,3:	-1344.648746	25.191199	-1683.819	-1256.609	2436.395575	790.54132	-333.3529	2752.2883
12									
13									
14									
15									
16									
17	001A	920.6045244	-	508.47235	1058.5074	126219.6294	-	38763.656	241445.24
18	002B	900.7643736	-	370.12707	1495.9564	12778.3046	-	5778.5109	24736.313
19	003C	941.4850815	-	808.747	1093.7426	181961.7579	-	139097.36	209230.02
20	004D	822.6175519	-	707.1929	1140.3613	31001.44173	-	21945.977	41554.684

Model Parameters
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	A	R	S	T	U	V	W	X	Y	Z
1	UKPDS Outcomes									
2	Version 2.0 © Isis Inn									
3										
4	ID	Total cost	MCE	95% CI		Expected utility by simulated year				
5	All:	53735.47176	504.63236	47293.703	64495.655	0.3694728	0.2413825	0.1658424	0.1107549	0.0702172
6	Group 1:	52741.9606	791.98472	45982.585	63314.739	0.3710726	0.2379102	0.1616192	0.1071099	0.0669384
7	Group 2:	54754.91583	820.99188	48005.189	64788.282	0.3673398	0.2426356	0.1680801	0.1126413	0.0718432
8	Group 3:	53663.169	1081.2844	48761.37	65342.278	0.3705001	0.2454114	0.1694201	0.113926	0.0732008
9	Difference 1,2:	-2012.955231	674.00963	-4176.528	-75.46529	0.0037328	-0.004725	-0.006461	-0.005531	-0.004905
10	Difference 1,3:	-921.2084029	830.7812	-4340.383	-151.1241	0.0005725	-0.007501	-0.007801	-0.006816	-0.006262
11	Difference 2,3:	1091.746828	807.10515	-1823.13	1268.8176	-0.00316	-0.002776	-0.00134	-0.001285	-0.001358
12										
13										
14										
15										
16										
17	001A	127140.2339	-	39272.129	242452.6	0.5644638	0.3339635	0.1702507	0.06277	-0.007662
18	002B	13679.06897	-	6189.9489	26366.571	0.3068357	0.0594133	-0.010841	-0.032313	-0.039206
19	003C	182903.243	-	140011.25	210258.74	0.7439952	0.6484305	0.5791915	0.5214449	0.4394889
20	004D	31824.05928	-	22708.416	42596.443	0.5253865	0.2811034	0.1217262	0.0080521	-0.057721

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	A	CN	CO	CP	CQ	CR	CS	CT	CU	CV	CW
1	UKPDS Outcomes										
2	Version 2.0 © Isis Inn										
3											
4	ID	Therapy cost by simulated year									
5	All:	395.58487	305.8068	188.70333	160.0112	136.06966	48.950389	41.61249	35.330436	30.278345	32.032716
6	Group 1:	283.36554	214.45852	2.1796949	1.7283604	1.599749	1.4236261	1.1527867	0.9366076	0.8193329	0.8309049
7	Group 2:	417.45328	324.47941	275.70074	234.83791	199.7886	1.2242649	1.1634735	1.049187	1.0318092	0.9913093
8	Group 3:	560.32756	438.29466	368.64158	310.84982	263.93805	224.35753	190.60281	161.79171	138.37987	146.64937
9	Difference 1,2:	-134.0877	-110.0209	-273.521	-233.1096	-198.1889	0.1993612	-0.010687	-0.112579	-0.212476	-0.160404
10	Difference 1,3:	-276.962	-223.8361	-366.4619	-309.1215	-262.3383	-222.9339	-189.45	-160.8551	-137.5605	-145.8185
11	Difference 2,3:	-142.8743	-113.8152	-92.94084	-76.0119	-64.14945	-223.1333	-189.4393	-160.7425	-137.3481	-145.6581
12											
13											
14											
15											
16											
17	001A	439.61353	354.73407	4.5097135	6.5358167	12.629598	16.270013	15.719819	13.289702	11.005965	7.4409391
18	002B	340.57971	191.36969	126.27198	78.4298	58.938122	44.742535	19.649774	11.391173	11.005965	11.161409
19	003C	461.35266	403.74338	4.5097135	4.3572111	4.2098658	6.1012548	7.8599096	5.6955867	9.1716372	13.021644
20	004D	427.53623	331.3963	4.5097135	6.5358167	8.4197317	8.1350064	7.8599096	3.7970578	3.6686549	3.7204696

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	A	FF	FG	FH	FI	FJ	FK	FL	FM	FN	FO
1	UKPDS Out										
2	Version 2.0 © Isis Inn										
3		Complication cost by simulated year									
4	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
5	All:	8797.9149	6902.0832	5745.0116	4843.4433	4107.9784	3496.7565	2975.8057	2528.5349	2148.4896	2319.98
6	Group 1:	9140.419	6972.734	5750.6792	4834.2925	4092.8131	3472.0378	2938.9798	2504.291	2135.2828	2283.7524
7	Group 2:	8591.6764	6901.8285	5800.9558	4914.746	4183.6673	3583.9463	3073.0803	2608.9457	2218.3298	2386.389
8	Group 3:	8553.6787	6773.3162	5630.9426	4728.0116	3995.4184	3380.3532	2862.8563	2423.8294	2043.1886	2263.1506
9	Difference 1,2:	548.74267	70.905474	-50.27665	-80.45347	-90.85422	-111.9085	-134.1005	-104.6547	-83.04692	-102.6365
10	Difference 1,3:	586.74035	199.41782	119.73659	106.28094	97.394668	91.684667	76.123452	80.461634	92.094237	20.601854
11	Difference 2,3:	37.997675	128.51235	170.01324	186.73441	188.24888	203.59318	210.22395	185.11633	175.14115	123.23839
12											
13											
14											
15											
16											
17	001A	28759.227	22642.699	17738.868	13977.175	11543.932	8985.2041	6023.709	3953.6371	2737.088	2404.8222
18	002B	5766.314	2238.694	1573.4526	1200.4814	865.27477	613.11917	147.54622	93.20258	154.83191	90.314399
19	003C	27936.396	24570.599	21754.218	19689.165	16874.974	14079.74	12085.696	10735.11	9339.5625	8300.8587
20	004D	7185.8019	5487.4373	4371.6351	3532.8355	2689.2455	2221.6743	1698.7858	1030.1797	644.59367	552.8841

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	A	HX	HY	HZ	IA	IB	IC	ID	IE	IF
1	UKPDS Out									
2	Version 2.0 © Isis Inn									
3		Total cost by simulated year								
4	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
5	All:	9193.4997	7207.89	5933.7149	5003.4545	4244.048	3545.7068	3017.4182	2563.8654	2178.768
6	Group 1:	9423.7846	7187.1925	5752.8589	4836.0209	4094.4128	3473.4615	2940.1326	2505.2276	2136.1022
7	Group 2:	9009.1296	7226.3079	6076.6566	5149.5839	4383.4559	3585.1706	3074.2438	2609.9949	2219.3616
8	Group 3:	9114.0062	7211.6108	5999.5842	5038.8614	4259.3565	3604.7107	3053.4591	2585.6211	2181.5685
9	Difference 1,2:	414.65493	-39.11542	-323.7977	-313.563	-289.0431	-111.7091	-134.1112	-104.7673	-83.25939
10	Difference 1,3:	309.77833	-24.41831	-246.7253	-202.8405	-164.9436	-131.2492	-113.3266	-80.39346	-45.4663
11	Difference 2,3:	-104.8766	14.697104	77.072396	110.72251	124.09943	-19.54008	20.784615	24.373816	37.793091
12										
13										
14										
15										
16										
17	001A	29198.841	22997.433	17743.378	13983.711	11556.562	9001.4741	6039.4288	3966.9268	2748.094
18	002B	6106.8937	2430.0637	1699.7246	1278.9112	924.2129	657.8617	167.196	104.59375	165.83787
19	003C	28397.749	24974.342	21758.727	19693.522	16879.183	14085.841	12093.556	10740.806	9348.7341
20	004D	7613.3382	5818.8336	4376.1448	3539.3713	2697.6652	2229.8093	1706.6458	1033.9768	648.26232

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Bootstraps Worksheet

This worksheet (Figure 15) tabulates estimated mean Life expectancy, Total quality-adjusted life expectancy (QALE), Therapy cost, Cost of complications, Total cost by bootstrap replication. The number of results reported depends on the number of bootstrap replications requested with each result showing the mean value for that bootstrap averaged across the total number of loops (Monte Carlo trials) requested. Overall values are provided together summary data for each group, and the group differences (1 vs. 2, 1 vs. 3, 2 vs. 3).

Figure 15: the Bootstraps worksheet (All)

	A	B	C	D	E	F
1	UKPDS Outcomes Model : Bootstraps					
2	Version 2.0 ©	Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)				
3						
4		All				
5	Bootstrap Number	Life expectancy	Total QALE	Therapy cost	Cost of complications	Total cost
6	1	3.209042242	0.766750624	1345.692104	48979.73683	50325.42893
7	2	3.754437213	0.525426856	1446.304246	59425.3435	60871.64774
8	3	3.168276734	0.499175872	1391.534314	52942.98333	54334.51764
9	4	3.521507581	0.570541835	1411.053872	53338.34996	54749.40383
10	5	3.548451272	0.546782611	1436.726716	54167.56185	55604.28857
11	6	4.540811721	-1.786418606	1731.658711	64510.01601	66241.67472
12	7	3.530875238	0.295444632	1422.462072	53403.93409	54826.39617
13	8	3.375044823	0.746818408	1364.536056	54939.24638	56303.78244
14	9	3.402115656	0.641459695	1367.964201	50671.95518	52039.91938
15	10	3.669577115	0.454896566	1430.136367	55498.52612	56928.66248
16	11	3.049746786	0.768390782	1333.854763	45955.54653	47289.4013
17	12	3.212903515	0.679794923	1378.335313	49789.75654	51168.09185
18	13	3.043463186	0.638019765	1325.469093	45708.76983	47034.23893
19	14	3.552859449	0.822568154	1414.690622	52546.48706	53961.17769

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Figure 15: the Bootstraps worksheet (Group 1)

	A	G	H	I	J	K
1	UKPDS					
2	Version 2.0 ©					
3						
4		Group 1				
5	Bootstrap Number	Life expectancy	Total QALE	Therapy cost	Cost of complications	Total cost
6	1	3.108990616	0.754994496	504.4437201	48078.62598	48583.0697
7	2	3.67033677	0.528223184	531.9890168	59136.63783	59668.62685
8	3	3.073719338	0.527099066	542.295325	52288.96951	52831.26483
9	4	3.416201364	0.549834192	518.3883721	52833.22389	53351.61226
10	5	3.416316022	0.529769848	543.4304981	53135.29793	53678.72842
11	6	4.395802063	-1.62339541	713.0522002	64082.81389	64795.86609
12	7	3.44062564	0.339104243	531.3447564	53045.66262	53577.00737
13	8	3.253855446	0.72828813	504.8426918	54522.02994	55026.87263
14	9	3.325429578	0.604642353	506.502775	50332.94185	50839.44462
15	10	3.559902571	0.479900643	519.1050887	55091.65209	55610.75718
16	11	2.96386507	0.732708083	517.7822647	45482.98919	46000.77145
17	12	3.115349156	0.661593461	530.3675849	48948.53665	49478.90424
18	13	2.93169256	0.618470101	504.6002093	45006.874	45511.47421
19	14	3.429485406	0.795428001	514.9528566	51570.20647	52085.15933

Model Parameters
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Event Worksheets

A worksheet is generated for each of the following events:

- IHD (Ischaemic Heart Disease)
- MI (Myocardial Infarction)
- Heart failure
- Stroke
- Amputation
- Blindness
- Renal failure

- Ulcer
- All Death
- CVD Death
- Other Death

These worksheets tabulate Event rate and Long-term history rate together with their respective 95% confidence intervals, for each subject specified and for each simulated year. Overall values for the population are provided, as well as summary data for each group, and the group differences (1 vs. 2, 1 vs. 3, 2 vs. 3).

The *per*-subject values are calculated by dividing the total simulated number of events by the total number of loops (Monte Carlo trials) (see 'Number of loops'). Note that a subject may have events such as a myocardial infarction in a particular year as well as a death: this indicates the event was fatal.

Figure 16; the Risk Factor worksheet

	A	B	C	D	E	F	G	H	I	J
1	UKPDS Outcomes Model : IHD									
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)									
3		Event rate by simulated year (point estimate)								
4	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
5	All:	0.0003906	0.0002083	0.0003125	0.000651	0.0005729	0.000625	0.0007813	0.0005469	0.0004688
6	Group 1:	0.0008	0.0004667	0.0002	0.0006667	0.0008667	0.0008667	0.0012667	0.0004667	0.0008
7	Group 2:	0.0001316	6.579E-05	0.0003947	0.0004605	0.0003947	0.0004605	0.0005263	0.0004605	0.0002632
8	Group 3:	0.000122	0	0.0003659	0.0009756	0.0003659	0.0004878	0.0003659	0.0008537	0.0002439
9	Difference 1,2:	0.0006684	0.0004009	-0.000195	0.0002061	0.0004719	0.0004061	0.0007404	6.14E-06	0.0005368
10	Difference 1,3:	0.0006678	0.0004667	-0.000166	-0.000309	0.0005008	0.0003789	0.0009008	-0.000387	0.0005561
11	Difference 2,3:	9.628E-06	6.579E-05	2.888E-05	-0.000515	2.888E-05	-2.73E-05	0.0001605	-0.000393	1.926E-05
12		Kaplan-Meier (KM) event-free survival								
13	All:	0.9996094	0.9993266	0.9988156	0.9975499	0.9962341	0.9945494	0.9920846	0.9900701	0.9880584
14	Group 1:	0.9992	0.9985506	0.9982142	0.9968785	0.9948383	0.9924379	0.9883343	0.9865658	0.9830223
15	Group 2:	0.9998684	0.9997803	0.999145	0.998266	0.9973698	0.9961434	0.9945117	0.9928495	0.9917454
16	Group 3:	0.999878	0.999878	0.9992923	0.9974323	0.9966111	0.9953297	0.9941926	0.9910886	0.9900567
17	001A	0.04	0	0	0.01	0.03	0.01	0	0.01	0
18	002B	0	0	0	0	0	0	0	0	0
19	003C	0.02	0.01	0	0	0.01	0.01	0.02	0	0.02
20	004D	0.01	0.01	0.01	0.01	0.02	0	0.01	0.01	0.01

	A	HD	HE	HF	HG	HH	HI	HJ	HK	HL
1	UKPDS Outcomes Model : IHD									
2	Version 2.0 © Isis Innovation Ltd 2015 (http://www.dtu.ox.ac.uk/outcomesmodel)									
3		Long term history rate by simulated year (point estimate)								
4	ID	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
5	All:	0.0001823	0.0002865	0.0004427	0.000651	0.0005729	0.0005729	0.0004948	0.0005469	0.0004688
6	Group 1:	0.0002667	0.0004667	0.0008	0.0012	0.0011333	0.001	0.0009333	0.001	0.0008667
7	Group 2:	0	0.0001316	0.0001974	0.0003289	0.0001974	0.0002632	0.0002632	0.0002632	0.0002632
8	Group 3:	0.0003659	0.0002439	0.0002439	0.0002439	0.0002439	0.0003659	0.000122	0.0002439	0.000122
9	Difference 1,2:	0.0002667	0.0003351	0.0006026	0.0008711	0.000936	0.0007368	0.0006702	0.0007368	0.0006035
10	Difference 1,3:	-9.92E-05	0.0002228	0.0005561	0.0009561	0.0008894	0.0006341	0.0008114	0.0007561	0.0007447
11	Difference 2,3:	-0.000366	-0.000112	-4.65E-05	8.504E-05	-4.65E-05	-0.000103	0.0001412	1.926E-05	0.0001412
12		Kaplan-Meier (KM) event-free survival								
13	All:									
14	Group 1:									
15	Group 2:									
16	Group 3:									
17	001A	0	0	0	0	0	0	0	0	0
18	002B	0	0.01	0.02	0.03	0.02	0.01	0	0	0
19	003C	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.02	0.02
20	004D	0	0	0	0.01	0.01	0.01	0.01	0.01	0

KMPlotSheet Worksheet

This worksheet (Figure 17) derives the Kaplan-Meier estimates by year of simulation for each type of event into a single worksheet for plotting purposes.

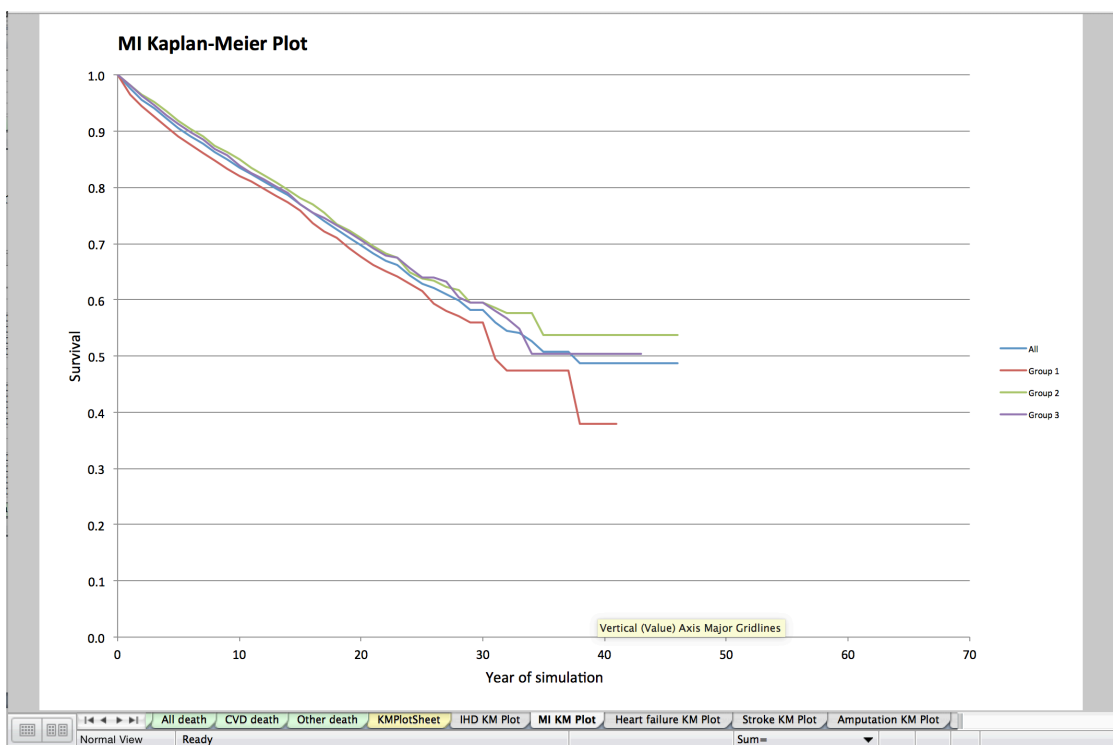
Figure 17: the KMPlotSheet, including year 0

[illegible]

KM Plot Worksheets

These worksheets (Figure 18) provide Kaplan-Meier survival plots by year of simulation for each event. They are generated for each of the events simulated by the model. (See Event Worksheets above).

Figure 18: KM Plot, including year 0



Worked Examples

These examples are provided as a practical guide to using OM2 and to illustrate some of the new features.

EXAMPLE #1

To determine the likely impact of a fixed difference in HbA_{1c} values over time, say 11.0% *versus* 7.0%, on Life Expectancy and Quality Adjusted Life Expectancy for a fifty-five year old patient with type 2 diabetes of five year's duration, proceed as follows:

Step 1: Enter patient characteristics

Using the *Inputs* worksheet, enter characteristics for two patients that have identical risk-factor levels for all but HbA_{1c} (see table 1)

Table 1: Patient characteristics

Demographic characteristics	Value	
ID for subject one	1	
ID for subject two	2	
Group for subject one	1	
Group for subject two	2	
Ethnicity	1	
Gender	M	Male
Current age	55	Years
Duration of T2DM	5	
Weight	91	(kg)
Height	1.74	(meters)
Risk factor values		
Atrial fibrillation (AF)	N	(No)
Peripheral vascular disease (PVD)	N	(No)
Current smoker	N	(No)
Micro/macroalbuminuria (albuminuria)	N	(No)
HDL cholesterol	1.22	(mmol/l)
LDL cholesterol	2.59	(mmol/l)
Systolic blood pressure	133.6	(mmHg)
HbA _{1c} for subject one	11.0	(%)
HbA _{1c} for subject two	7.5	(%)
Heart rate	81	(bpm)
White blood cell count (WBC)	6.85	(x 10 ⁻⁶ ml)
Haemoglobin	14.10	(g/dl)
Glomerular filtration rate (eGFR)	80	(ml/min/1.73m ²)
Pre-existing events		
History of ischemic heart disease	N	(No)
History of congestive heart failure	N	(No)
History of amputation	N	(No)
History of blindness in one eye	N	(No)
History of stroke	N	(No)
History of myocardial infarction	N	(No)

History of ulcer	N	(No)
Discounting start year (both patients)	0	

Step 2: Risk factor time paths

For simplicity, assume that all risk factors remain constant through the entire simulation. Hence, choose method ‘1’ to populate the sheet (1=‘Match initial values’) in all risk factor worksheets:

- Smoking status
- HDL
- LDL
- Systolic BP
- HbA1c
- PVD
- AF
- Weight
- Albuminuria
- Heart rate
- WBC
- Haemoglobin
- eGFR

Step 3: Set up simulation

Go to the *Model Parameters* worksheet. To obtaining point estimates in an initial simulation we will deal only with first order uncertainty. Set the “Number of subjects” to 2 by choosing the last row to be ‘18’, the “Number of loops” to 10,000 to reduce Monte Carlo error, the “Number of years simulated” to 70, the ‘Number of processes to use’ to 1, and the initial and subsequent QALE/life expectancy and total costs “discount rate” to 0. At this stage we will not estimate confidence intervals so set the “Number of bootstraps” to 0.

Set up ‘Therapy costs prior to complication’ and ‘Therapy cost post complication’ to £500 for groups 1 and 2 and the number of years to apply to 70. This ensures that patient one and two will face the same therapy costs during the entire simulation period. Now, assume that the costs and utilities associated with diabetes-related complications remain constant through the whole simulation period. To do this, set the age limit of the first age group to 200 (cell B24) and clear the value for the other groups.

Once all the above is done, click on ‘Populate annual risk factor sheets’ and then ‘Verify model data’.

Step 4: Run the simulation

If no errors were identified use the *Inputs Check* worksheet to confirm the values for all Risk Factors by group and by year of simulation. If all is well save the Excel file and close it.

Now, open the OM2 Controller Application Interface, select ‘File’ and then ‘Open’ your file. Select start and wait until is finished. Now open the resulting Excel file (will have the same name plus Outputs at the end).

The Life Expectancy for subject one should be approximately 22.7 years (16.2 QALYs) and for subject two, with the lower HbA_{1c}, somewhat greater at approximately 24.0 years (17.9 QALYs). The total costs should be £36,577 for

subject one and £36,024 for subject two. The difference in life expectancy between patient one and two should be -1.3 years and the difference in total costs should be £553. Estimates may differ slightly between simulations as the Outcomes model may have used a different set of random numbers.

It is also possible to examine cumulative events rates over the years specified in the simulation. For example, the MI worksheet contains the expected incidence and KM event-free survival myocardial infarction for both groups. The expected cumulative incidence of events can be estimated by summing the event rates at each year. These plateau at around 0.30 for patient one and 0.23 for patient two around 40th year of the simulation as almost all patients are dead and therefore cannot have an MI.

EXAMPLE #2

We may also want to undertake a simulation to estimate the cost-effectiveness of a hypothetical new therapy for HbA_{1c} compared to standard care. The following assumptions are made:

- The target population of the new therapy is fully represented using a single male individual with an initial HbA_{1c} value of 7.5% and characteristics listed in Table 1;
- New treatment costs £500 per year and is effective at decreasing HbA_{1c} to 6.5% and keeping it constant through a patient's lifetime;
- Standard care for HbA_{1c} costs £100 per year but allows HbA_{1c} to increase by 1% every year.

To undertake this type of simulation proceed as follows:

Step 1: Enter patient characteristics

Using the *Inputs* worksheet, change the two patients set out in Example #1 to have HbA_{1c} levels of 7.5%. Group 1 will receive the new therapy whereas Group 2 will receive standard care.

Step 2: HbA_{1c} time path

Go to the *HbA_{1c} worksheet*. Change *Method* to '2' (linear regression with slope m and constant c) and *Replace existing* to 'N'. Now, change the slope coefficient m to be 1.00 for Group 1 ('new therapy' group) and 1.01 for group 2 (i.e. HbA_{1c} value will increase by 1% every year in the standard care group). For the first subject, enter 6.5 for year 1 and copy this value across the row to year 70. For the second subject, clear all HbA_{1c} values in that worksheet.

Step 3: Run model

Go to the *Model Parameters* worksheet, change the discount rate for both QALE and costs to be 3.5% for 70 years to allow a more realistic economic evaluation. Now, set 'Therapy costs prior to complication' and 'Therapy cost post complication' to £500 for group 1 and £100 for group 2 and the 'number of years to apply' to 70. Click on 'Populate annual risk factor sheets' and then 'Verify model data'.

Use *Inputs Checks* to make sure the HbA_{1c} time path in both groups is correctly modelled, save the Excel file and close it. Now, open the Controller Application Interface, select 'File' and then 'Open' the saved file. Select start and wait until is finished. Now, open the resulting Excel file (will have the same name plus Outputs at the end).

Look at the *Outputs* worksheet. Group 1's (quality adjusted) life Expectancy is higher, at around 15.2 years and 11.6 QALYs, relative to Group 2, at around 15.0 years and 11.3 QALYs. Total costs are also higher for Group 1 (£22,326) compared to Group 2 (£16,632). Hence, the new therapy is more effective but more costly than standard care. The incremental QALYs of the new therapy (Group 1) relative to standard care (Group 2) are 0.26 QALYs. The incremental costs of the new therapy relative to standard care are £5,694. The incremental cost-effectiveness ratio of the new therapy relative to standard care is then estimated at £21,877 per QALY gained.

EXAMPLE #3

To obtain confidence intervals for Life Expectancy, Quality of Life Expectancy and costs for Example #2 proceed as follows:

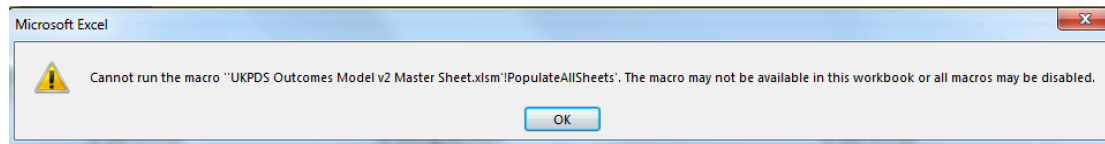
Step 1

Go to the *Model Parameters*. Keep the "Number of loops" at 10,000 and change the "Number of bootstraps" to 1,000. Save the Excel file and run the model using Controller Application Interface. The simulation will take a little longer to run (approximately 20 minutes on PC with a Pentium IV processor). Go to the *Outputs* worksheet. The Life Expectancy, QALE and costs will now have 95% confidence intervals around them. Go to the *Bootstraps* worksheet. The 1,000 bootstraps for life expectancy, QALE and costs are made available by group. These can be used to plot pairs of incremental costs and QALE in the cost-effectiveness plane and estimate cost-effectiveness acceptability curves.

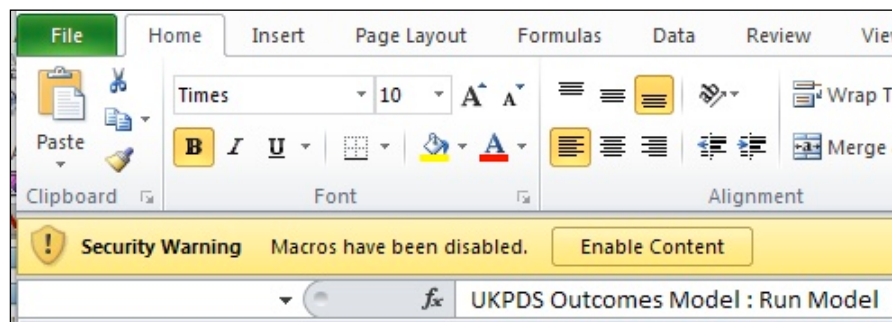
Appendix 1 : Enabling VBA macros in Microsoft Excel

Microsoft office 2010 and 2013 for Windows

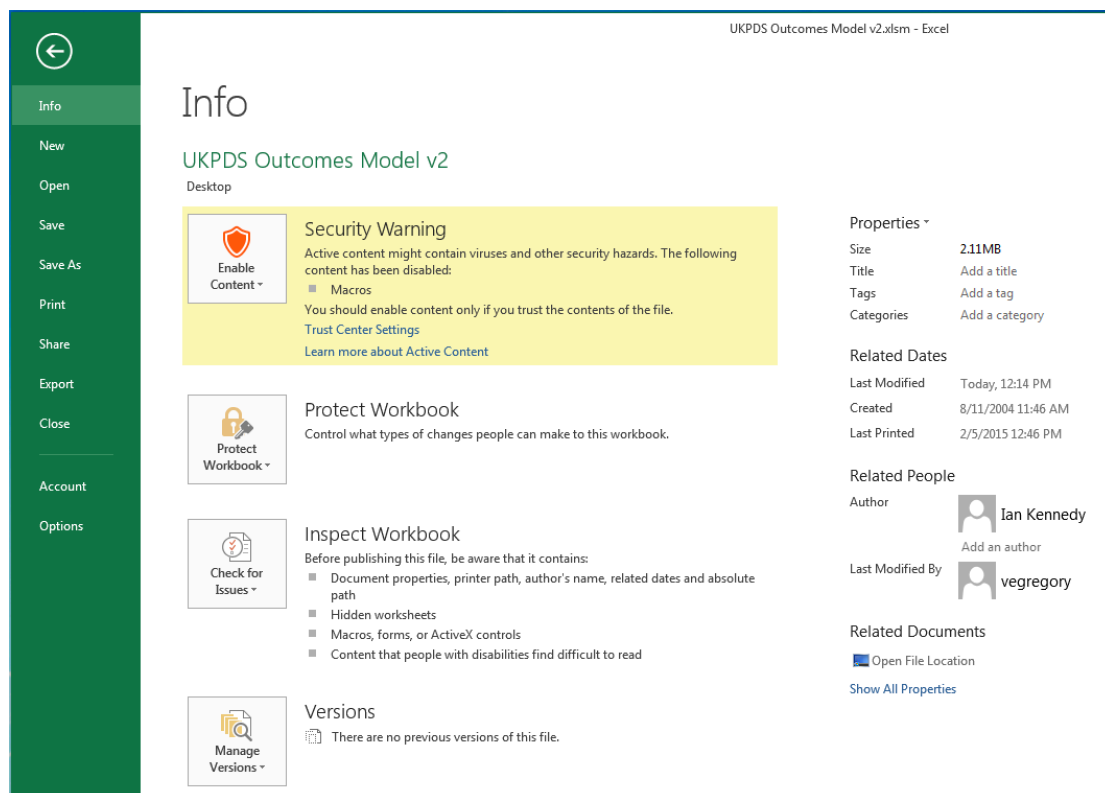
Opening the workbook in these versions and clicking any of the buttons on the Model Parameters worksheet will open the following dialog:



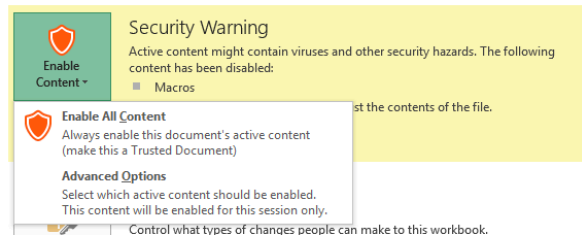
and a security warning appears at the top of the page:



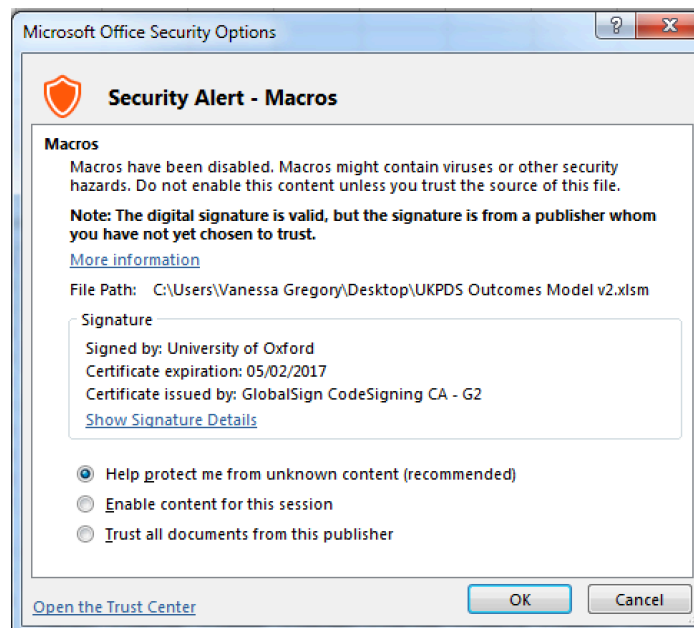
Click **File**. The **Microsoft Office Backstage** view appears. In the **Security Warning** area, on the **Enable Content** button, click the **down-arrow**.



Select **Advanced Options** to learn more about the publisher.



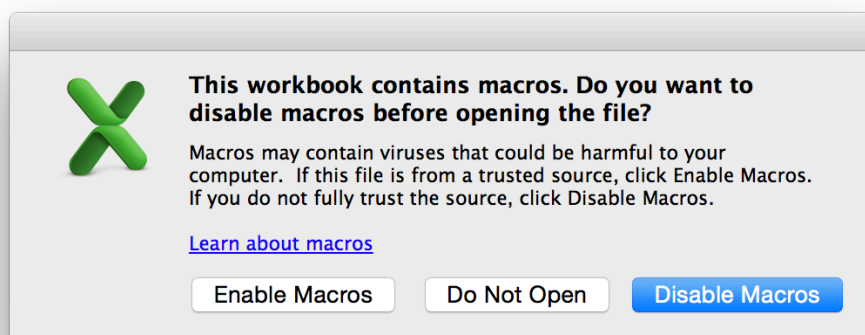
The following **Security Options** dialog will appear



Check the 'Always trust macros from this publisher' box Click OK. You will now be able to run the model. When the model is opened again, this dialog will not appear.

Microsoft Office 2011 for Macintosh

Each time you open an Excel file that contains macros the following dialog will show:



Click the Enable Macros button to enable the features.

References

1. Hayes AJ, Leal J, Gray AM, et al. UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia* 2013;**56**(9):1925-33.
2. UKPDS Group. UK Prospective Diabetes Study VIII: study design, progress and performance. *Diabetologia* 1991;**34**:877-90.
3. Clarke P, Gray A, Briggs A, et al. 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**:1747-59.
4. Alva M, Gray A, Mihaylova B, et al. The Effect of Diabetes Complications on Health-Related Quality of Life: The Importance of Longitudinal Data to Address Patient Heterogeneity. *Health Economics* 2014;**23**(4):487-500.
5. Alva ML, Gray A, Mihaylova B, et al. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). *Diabet Med* 2015;**32**(4):459-66.
6. Lung TW, Hayes AJ, Hayen A, et al. A meta-analysis of health state valuations for people with diabetes: explaining the variation across methods and implications for economic evaluation. *Quality of Life Research* 2011;**20**(10):1669-78.
7. Transplant NBa. Factsheet 7: Cost-effectiveness of kidney transplantation:. London, UK., 2012.
8. Kerr M. Foot Care for People with Diabetes: The Economic Case for Change.: NHS Diabetes, 2012.