The Michigan Model for Diabetes User Manual

Version 2.0
September 17, 2015

Produced by the University of Michigan
Michigan Center of Diabetes Translational Research (MCDTR) Disease Modeling Group
http://www.med.umich.edu/mdrtc/cores/MCDTR_MMCore/DiseaseModel/index.html

Condition of Use and Copyright

List of Abbreviations

HbA1c	Glycated hemoglobin
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
MI	Myocardial infarction
CHD	Coronary heart disease
CHF	Congestive heart failure
DR	Diabetic retinopathy
MMD	Michigan Model for Diabetes
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ACR	Albumin/creatinine ratio (for urine albumin test)
PTCA	Percutaneous transluminal coronary angioplasty
CABG	Coronary artery bypass graft
ACE-I	Angiotensin converting enzyme-inhibitor
ARB	Angiotensin receptor blocker
QALE	Quality-adjusted life expectancy
QALYs	Quality-adjusted life years
IEST	Indirect Estimation and Simulation Tool

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1. Introduction and Background

The Michigan Model for Diabetes (MMD) is a computerized disease model that enables the users to simulate the progression of diabetes over time, its complications (retinopathy, neuropathy and nephropathy), and its major comorbidities (cardiovascular and cerebrovascular disease), and death. Transition probabilities can be a function of individual characteristics, current disease states or treatment status. The model also estimates the medical costs of diabetes and its comorbidities, as well as the quality of life related to the current health state of the subject.

In contrast to other proposed models, the transition probabilities implemented in the MMD were obtained by synthesizing the published literature. Specifically, transition probabilities in the newly updated coronary heart disease sub-model that reflects the direct effects of medical therapies on outcomes were derived from the literature and calibrated to recently published population-based epidemiologic studies and randomized controlled clinical trials. This method not only allowed us to build a model without access to individual-level data from a long-term prospective study, but allowed us to update the model by incorporating data from new studies as they become available.

In addition, different from other proposed models, our model allows a user to control risk factor changes by defining treatment thresholds and compliance rates for hyperglycemia, dyslipidemia, and hypertension, and compliance to quitting smoking and taking aspirin. Given the fact that modern medicines have largely decreased the complication rate in type 2 diabetes through management of these risk factors, it is important to explicitly model these management strategies and allow users to modify them to match the specific scenarios that they are simulating.

Most of the risk equations adapted in the coronary heart disease sub-model and cerebrovascular disease sub-model are from the UKPDS Outcomes Model 1 (Appendix A, Reference 5), which was based on a population of newly diagnosed diabetics between 25 and 65 years of age that were followed for 14 years. These equations model race with only two categories, Caucasians and Blacks. In light of this, and recognizing that the other data sources for our model are studies that were conducted in the United States and Western Europe, and considering the difference in medical practice across countries, caution should be applied when model results are extrapolated to populations that differ significantly from the model target population: relatively young (25-79 years of age) Caucasians or Black populations with type 2 diabetes in the United States and Western Europe. Despite this, the IEST software which houses our model, allows users to adjust parameters to better suit their own situations. For example, when applying the model to a population in a country with less access to revascularization procedures, users can adjust the transition probabilities to match the revascularization procedure rates in their countries.

The current MMD software provides raw simulated data for all simulated individuals, e.g. risk factors, complications status, yearly medical cost and utility score for each simulated year. We provide SAS programs that can generate estimates of life expectancy, quality-adjusted life years and costs of complications for the working examples in Section 8. The provided SAS programs can also output longitudinal trajectories for important risk factors, cumulative event rates, and long term history rates. Using the raw results, users can also write their own programs to summarize other quantities of their own interest.

2. Changes in Version 2.0

The MMD has been substantially revised since its original publication in 2005 (Zhou et al., 2005) and is implemented by using newly developed software that models chronic diseases.

New features of the MMD include:

(1) Modeling disease progression through evolution of multiple biomarkers and risk factors
(2) An updated coronary heart disease sub-model that incorporates the possibility of recurrence of myocardial infarction (MI), congestive heart failure, and cardiac procedures either before or after MI
(3) Modeling modern diabetes treatment regimens and management for hyperglycemia, dyslipidemia, and hypertension
(4) Modeling direct benefits of medications and compliance.
(5) Updated transition probability tables for end stage renal disease
(6) Updated competing death table
(7) Updated cost and utility models

3. Download and Installation

In order to run the MMD, one has to download both the MMD files and a disease modeling software, the Indirect Estimation and Simulation Tool (IEST).

3.1. Download the disease modeling software IEST and Michigan Model for Diabetes

3.1.1. Installation of Python environment

The IEST software is written using Python language. It requires installation of Python version 2.7 and a few Python libraries as follows.

NOTE: This software has been tested on Microsoft Windows XP, Windows 7, and Linux. Note that other operating systems (such as OS X and other Windows versions) may work, yet were not fully tested.

Windows installation

- Visit http://python.org/ftp/python/2.7.2/python-2.7.2.msi (or http://python.org/download/releases/2.7.2/) and download Python version 2.7 for Windows.
- Visit http://downloads.sourceforge.net/wxpython/wxPython2.8-win32-unicode-2.8.12.1-py27.exe (or http://www.wxpython.org/download.php#stable) and download wxPython (Requires Python), a Unicode version suitable for Python version 2.7 for Windows 32 bit.
- Visit http://sourceforge.net/projects/numpy/files/NumPy/1.6.1/numpy-1.6.1-win32-superpack-python2.7.exe/download (or http://www.scipy.org/Download) and download the NumPy library (Requires Python), a version suitable for Python version 2.7 for Windows.
- Visit http://sourceforge.net/projects/scipy/files/scipy/0.10.0/scipy-0.10.0-win32-superpack-python2.7.exe/download (or http://www.scipy.org/Download) and download the SciPy library (Requires Python and NumPy), a version suitable for Python version 2.7.
- Visit http://code.google.com/p/sympy/downloads/detail?name=sympy-0.7.1.win32.exe (or http://code.google.com/p/sympy/downloads/list) and download the Sympy library (Requires Python), Version 0.7.1

OS X installation

- Python for OS X is included by default on all OS X installations.
- Install pip to assist with the installation of non-standard Python modules used by the IEST software by visiting the following webpage: http://pip.readthedocs.org/en/latest/installing.html and downloading the "get-pip.py" file. Save the file to your desktop.
- Open the application "Terminal" through Applications -> Utilities -> Terminal and issue the following commands:
  - sudo python ~/Desktop/get-pip.py
  - sudo pip install numpy
  - sudo pip install scipy
- Download wxPython2.8.12 ansi version (NOT unicode like Windows from above) by visiting the following webpage, and install the subsequent .dmg

file: http://sourceforge.net/projects/wxpython/files/wxPython/2.8.12.1/wxPython2.8-osx-ansi-2.8.12.1-universal-py2.7.dmg/download

3.1.2. IEST software and MMD installation

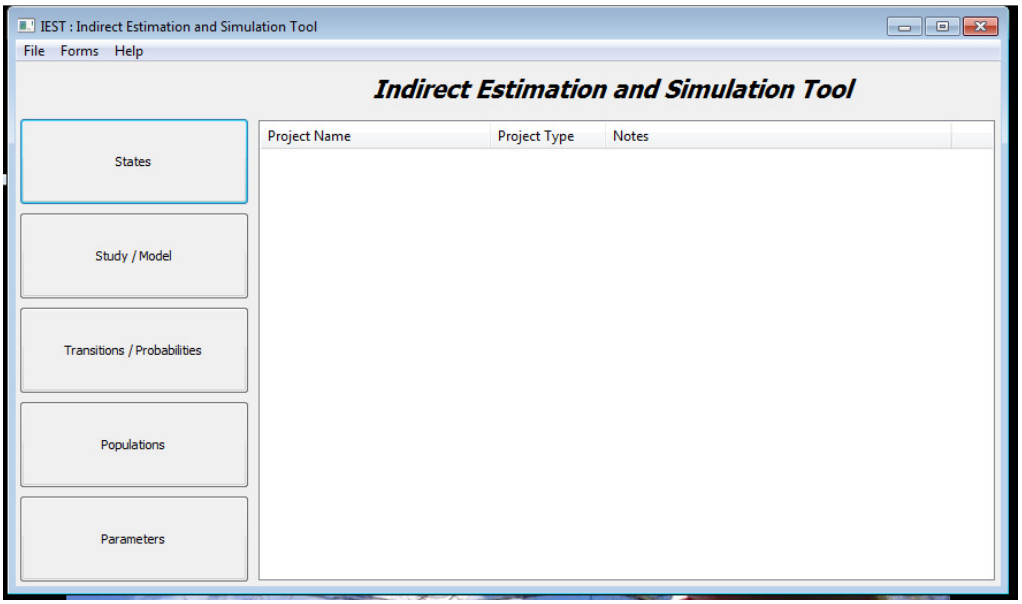
After Python environment has been properly installed:

Visit http://www.med.umich.edu/mdrtc/cores/DiseaseModel/model.htm to download the package that includes both IEST software and MMD. Downloading the file requires compliance to its license and registration.

- Extract the downloaded zip file archive to a directory of your choice. This will be your working directory.
- If using OS X or Linux, unzip the IEST software and issue the following command in the unzipped IEST working directory:
    - python Main.py

3.1.3. Running the IEST software

Open the working directory created during installation and double-click 'Main.py'. The main form of the system, titled 'Indirect Estimation and Simulation Tool', will open.

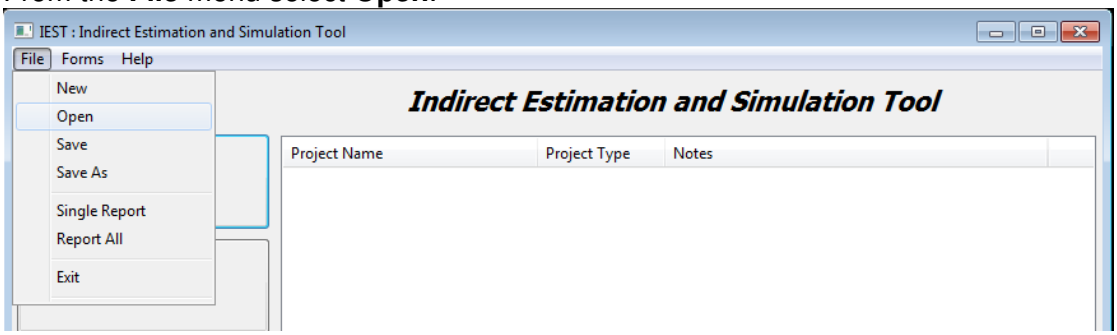


As the User Manual for MMD, this document does not include detailed information on IEST. To access the help system for IEST, click on the **Help** menu or click here.
For a set of videos tutorials for IEST please click here.

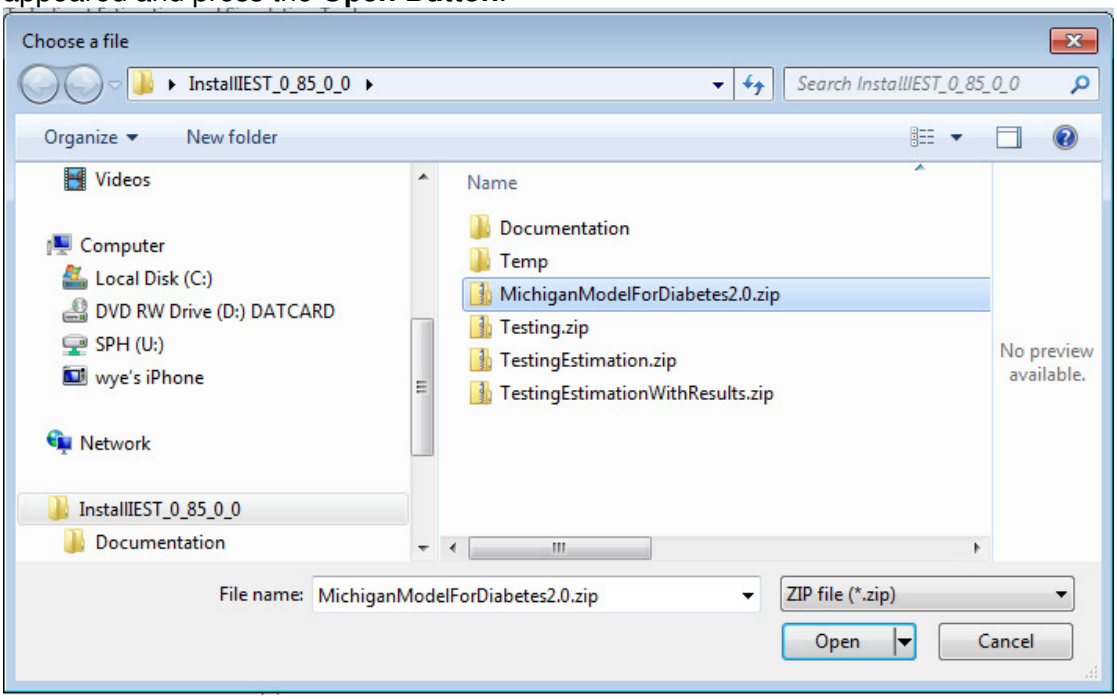
3.2. Loading the Michigan Model for Diabetes in the IEST software

To load the MMD in the IEST software, follow the steps below:

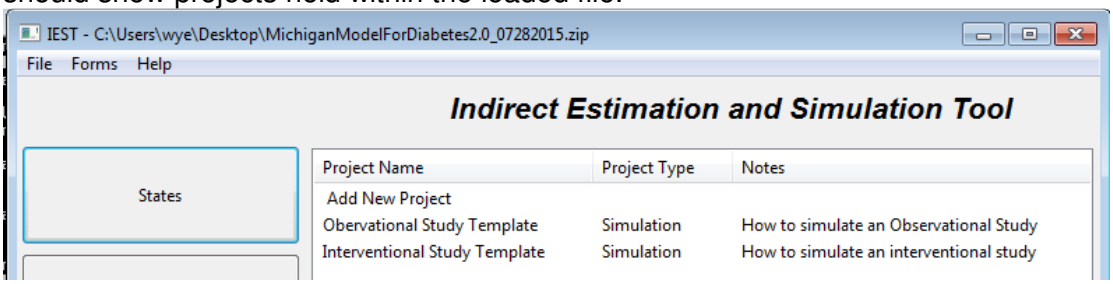
a) From the menu bar at the top of the main form, select **File**.
b) From the **File** menu select **Open**.



c) Select the requested filename/path of the zip file of MMD from the new window that appeared and press the **Open Button**.



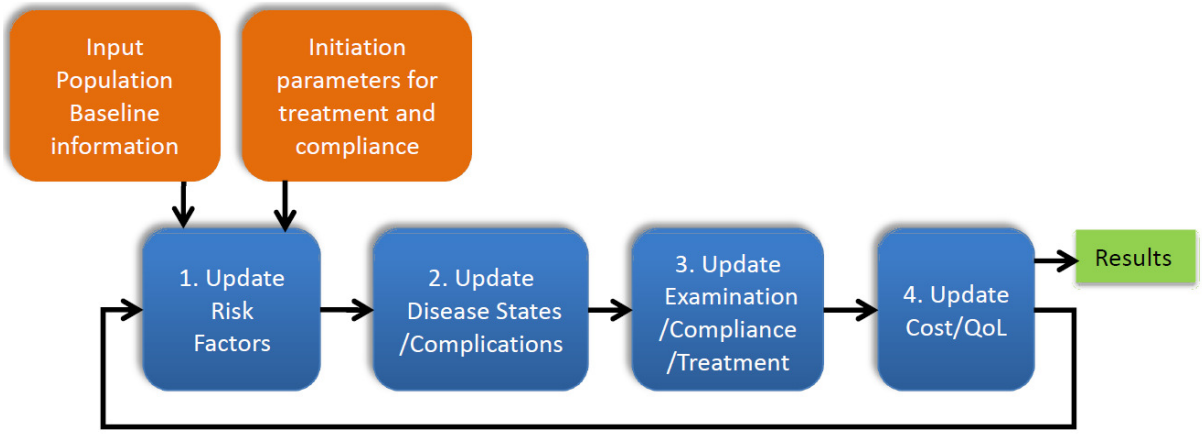
d) The label at the top of the windows should show the path of the file and the project list should show projects held within the loaded file.



4. Implementation of the Michigan Model for Diabetes in IEST

For each subject, the model software reads in or simulates the subject's baseline characteristics and then advances the subject through a specific number of years or until death. Each year, the model updates in the four stages as indicated by blue blocks in the following figure, including:

1) Update risk factors (i.e. weight/BMI, HbA1c, fasting glucose, systolic blood pressure (SBP)/diastolic blood pressure (DBP), lipids) according to treatment status and natural history of changes in glycaemia, blood pressure, and lipids.
   See Appendix A1 for details of model specification.
2) Update disease states and complications based on transition probabilities which can be functions of individual characteristics, current disease states or treatment status. See Appendix A1 for details of model specification.
3) Update treatments when certain risk factor passes pre-specified threshold or subject experiences a major complication event, taking account of pre-specified compliance parameters.
4) Assign cost and utility values for the specific year according to complication experiences.



The first year of this process differs for observational studies and intervention studies. For an observational study, the first step (updating risk factors) is skipped during the first year cycle so that all transition probabilities are calculated based on baseline characteristics. For an intervention study, risk factors will be changed according to treatment regimen used in the study to reflect the immediate intervention or "on trial" effect.

If you wish to use the default MMD model parameters, you only need to specify population baseline information and initial parameters (i.e., treatment threshold, maximum treatment level, and compliance rate) as model inputs. Please read **section 4.1** for instructions.

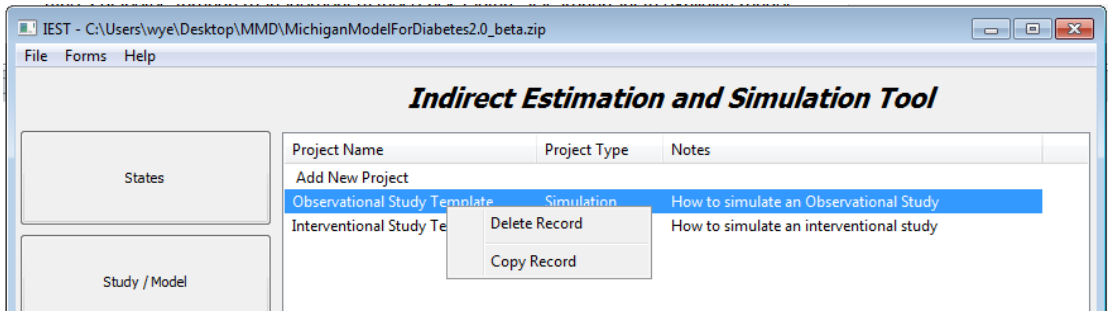
If you wish to further modify the MMD model parameters to suit your own situation please contact us at help.MichiganModelForDiabetes@umich.edu.

4.1. Running simulation using the default MMD

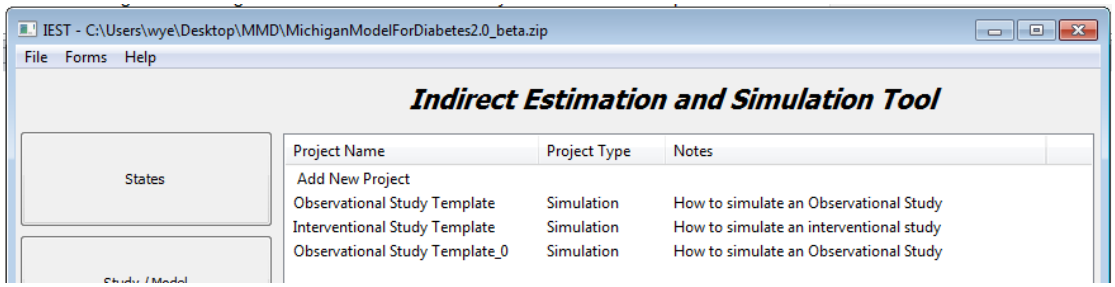
4.1.1. Start your own project

The MMD zip file includes two example projects, one observational study and one intervention study. To start your own project, do the following:

1) Make a copy of the example that matches your project.
   For example, if you wish to simulate an observational study, on the project list, right click the line for 'Observational Study Template'.

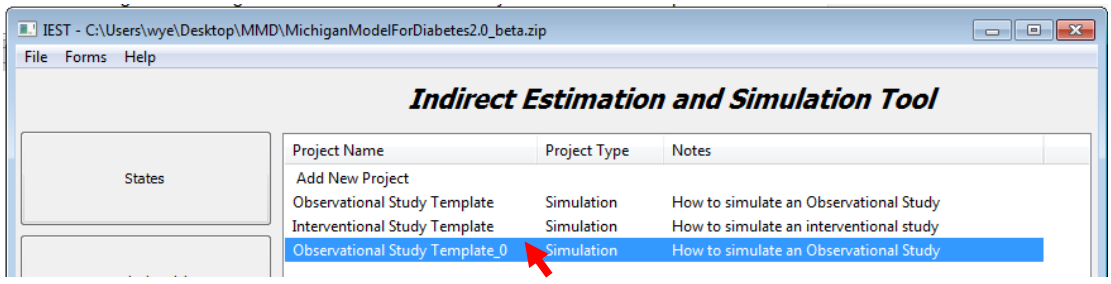


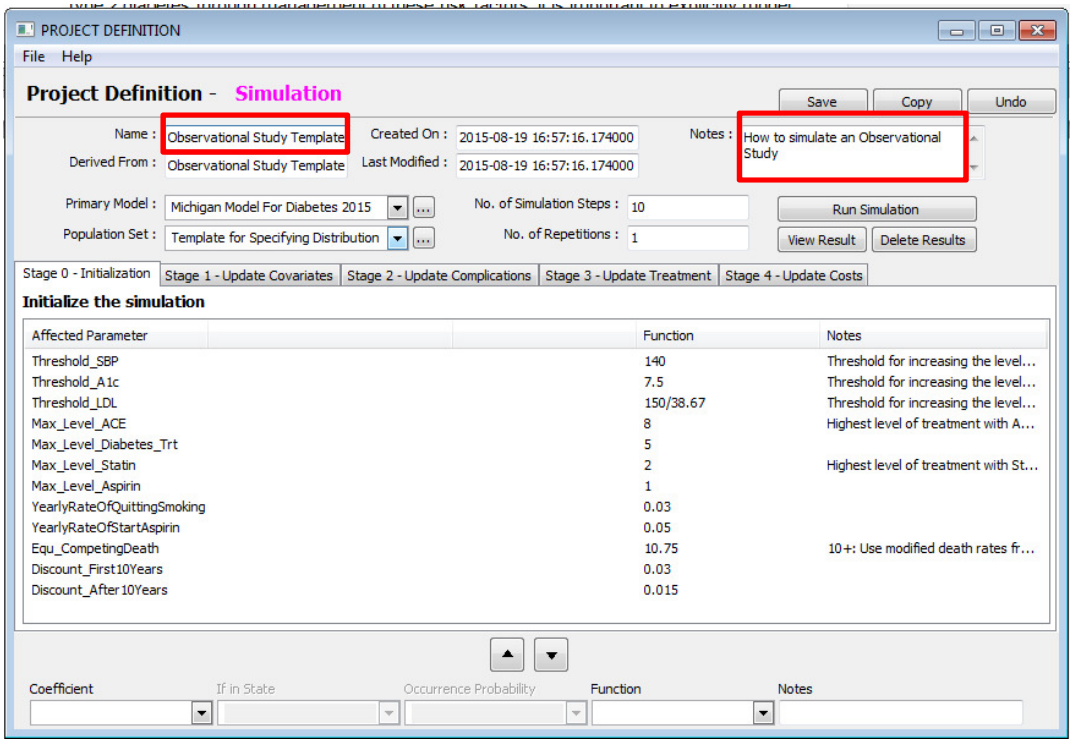
From the dropdown menu, select **Copy Record**. You should see a new project added to the list named as 'Observational Study Template_0'.



2) Change the name of the new project to your own.
   Double click on the line of the new project to open the popup window for PROJECT DEFINITION.

On the upper left corner of the PROJECT DEFINITION window, change the project name to your own. On the upper right corner, change the notes to your own, if desired.





Before modifying any parameters under the project window (including steps in 4.1.2 – 4.1.4), one needs to delete existing results using the **Delete Results** button. Otherwise no modifications on the project can be saved and need to be redone. This is a problem the future version of IEST will fix.

4.1.2. Defining general treatment parameters and compliance rate

There are five types of treatments and one behavior change modeled in MMD:

1) Treatment for hyperglycemia
2) Treatment for hypertension
3) Treatment for dyslipidemia
4) Beta-blocker
5) Aspirin therapy
6) Smoking cessation

In MMD, the change of treatment depends on four factors: levels of risk factors, disease history or diagnosis, the maximum level of treatment available, and patient's compliance characteristics.

1) The need for change of treatment or behavior:

The need for starting or intensifying treatments for hyperglycemia, hypertension, and dyslipidemia are triggered by a relevant risk factor passing the specific treatment threshold. The need for starting beta-blocker is triggered by a CVD event (CVD: myocardial infarction (MI), revascularization procedure, stroke, or heart failure) and

diagnosis of coronary artery disease (CAD). Aspirin and smoking cessation are recommended for all patients, especially subjects with CVD or CAD.

2) Compliance characteristics:
We assume each person has a fixed compliance profile for all the five types treatments, e.g. for each type of treatment, a patient either complies all the time or never complies with any prescriptions. For current smoker, the model does not assign a compliance status, i.e. all current smokers can potentially quit.

3) History of disease or diagnosis:
For the first three treatments (i.e., treatments for hyperglycemia, hypertension, and dyslipidemia), we also assume most patients are willing to comply with the need of treatment when they experience a CVD event. Among the subjects who are non-compliers but become willing to comply when they experience a CVD event when diagnosed with a CAD, they comply with 50% probability.

4) Maximum level of treatment:
There are a maximum of 5, 2, and 8 treatment levels available for hyperglycemia treatment, hypertension treatment, and dyslipidemia treatment, respectively. When the maximum level of treatment has been reached, no further intensification is available even if there is a need for that.

The following table shows the rule for each treatment/behavior change. See Appendix A2 for details on treatment regimens.

<table>
<tr><th>Treatment/behavior change</th><th>Start or intensification rules</th></tr>
<tr><td>Hyperglycemia:</td><td rowspan="3">For each of these treatments, if a complier's relevant risk factor (i.e., HbA1c for hyperglycemia, SBP for hypertension, LDL cholesterol for dyslipidemia) passes a user-specified threshold, the treatment will be started or intensified.

For patients who are non-compliant but become compliant when there is a CVD event, the treatment is started or intensified when the risk factor is higher than the threshold. For the same group of patients, if there is a need to start or intensify treatment and a diagnosis of CAD, they will comply with the treatment change with 50% probability.

The remaining patients will never start or intensify these treatments.</td></tr>
<tr><td>Hypertension:
ACE-I or ARB is started or intensified</td></tr>
<tr><td>Dyslipidemia:
Statin is started or intensified</td></tr>
<tr><td>Beta-blocker is started</td><td>For compliers, when there is a CVD event or the patient is diagnosed with CAD, the treatment will be started.
For non-compliers, treatment will never start.</td></tr>
</table>

Aspirin is started	Among subjects who are not currently on aspirin: For compliers, after a new CVD event or the patient is diagnosed with CAD, aspirin will be started. The remaining compliers are randomly assigned to start aspirin each year at a user-specified rate. For the non-compliers who become willing to comply with treatment when there is a CVD event, aspirin is started when there is a CVD event. For the same group of patients, if they are diagnosed with CAD, they will comply with the treatment change with 50% probability. The remaining patients will never start or intensify this treatment.
Smoking cessation:	When there is a new CVD event, a current smoker quits smoking. When CAD is diagnosed, a current smoker quits smoking with 50% probability. The remaining smokers quit smoking each year at a user-specified rate.

We further assume a hierarchical structure of patients for compliance. For ease of exposition, let's assume 90% of patients comply with all treatments when there is a CVD event, 80%, 70%, 60%, 50%, and 40% comply with treatment for hyperglycemia, beta-blocker, dyslipidemia, hypertension, and aspirin, respectively. This means 90% of patients are willing to comply with hyperglycemia treatment, dyslipidemia treatment, hypertension treatment, and aspirin when there is a CVD event. Among the above 90% of patients, 8 out of 9 (80% of the initial sample) comply with treatment for hyperglycemia regardless of their CVD complication history; among the 80% of compliers with treatment for hyperglycemia, 7 out of 8 (70% of the initial sample) comply with the prescription of beta-blocker, etc.; among the total population, 40% comply with all five treatments regardless of their CVD complication history. To implement the above treatment and compliance rules, the simulation program does the following. Before the start of the simulation cycle, each patient is assigned a treatment-specific compliance profile that includes six variables: one for compliance when there is a CVD event and five for treatment-specific compliance rates (i.e., one for each of five types of treatments.

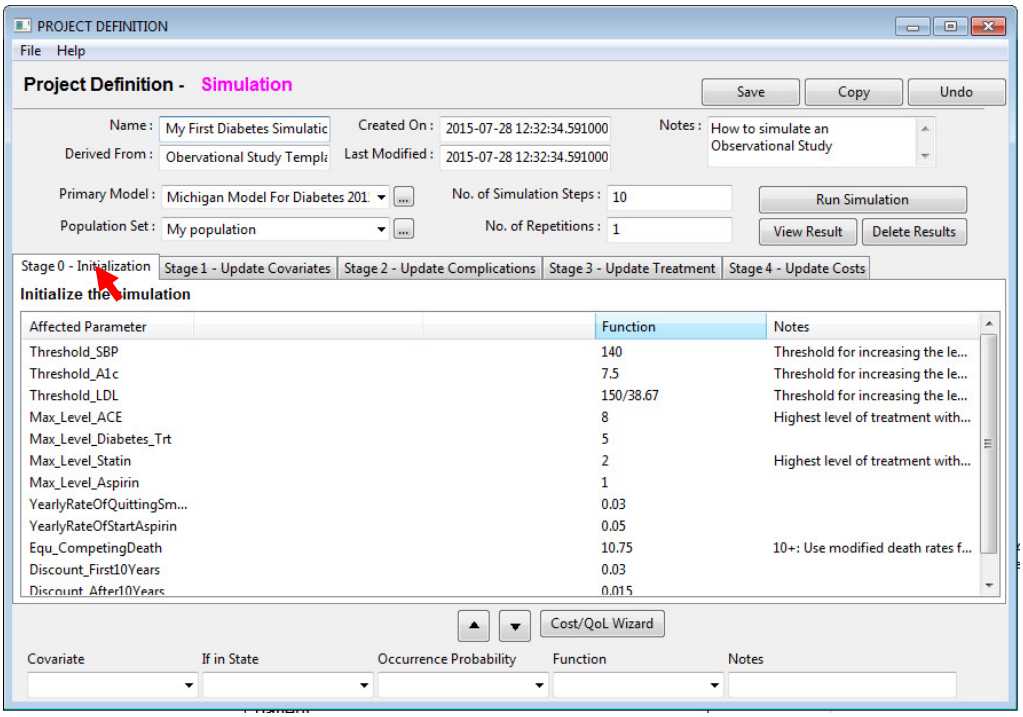
To set up the simulation, a user needs to specify the four following sets of parameters:

1) Treatment threshold parameters
2) Parameters for maximum level of treatment
3) Yearly rates for starting aspirin and quitting smoking
4) Compliance rate parameters

Next, we will show how to specify treatment- and compliance-related parameters.

Treatment Parameters

In the examples included in the MMD zip file, we have set the value for treatment-related parameters according to standard of practice in the US. To change them, click on "**Stage 0 – Initiation**" to bring the following tab to the front.



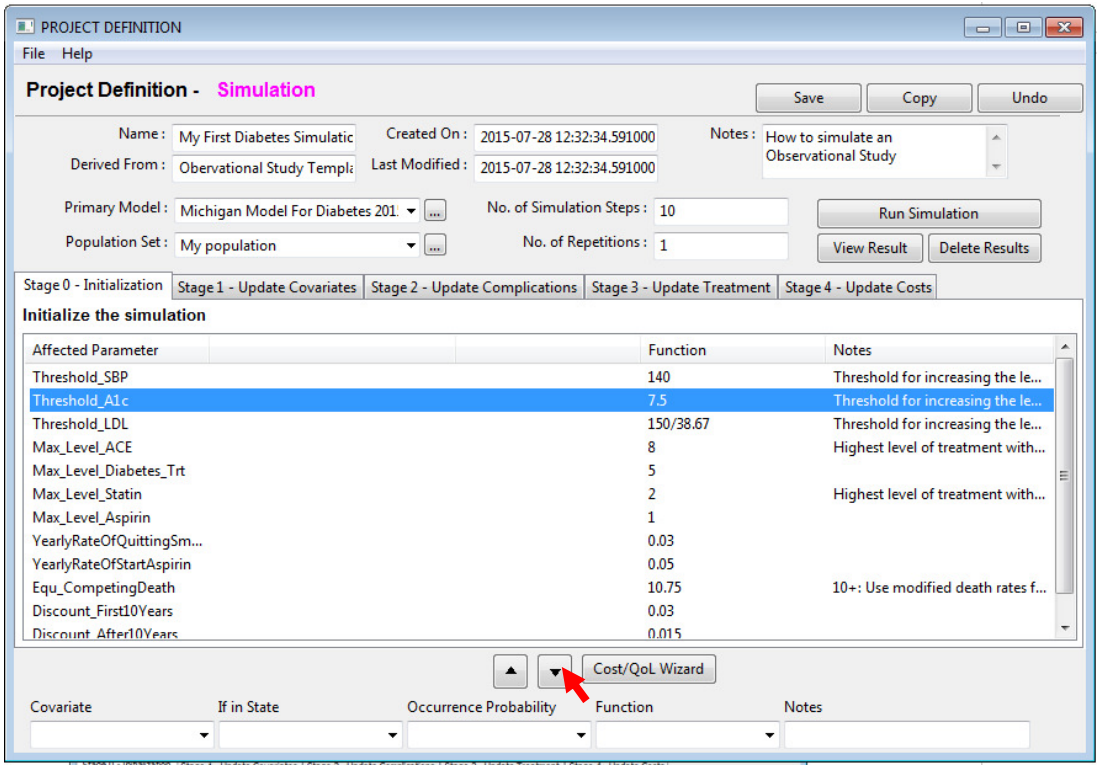
On this tag, there are eight parameters that are used to set up treatment thresholds, maximum levels of treatment allowed in the simulation, and yearly rate of quitting smoking and starting aspirin. See Appendix A2 for how treatments are specified in MMD. The eight parameters are described in the following table.

Parameters	Explanation
Threshold_A1c (%)	At the end of each year, if the HbA1c level is higher than the threshold level specified, anti-hyperglycemia treatment will be increased by 1 level for compliant patients.
Threshold_SBP (mmHg)	At the end of each year, if the SBP level is higher than the threshold level specified, treatment for hypertension treatment will be increased by 1 level for compliant patients.
Threshold_LDL (mmol/L)	At the end of each year, if the LDL level is higher than the threshold level specified, treatment for dyslipidemia will be increased by 1 level for compliant patients.
Max_Level_Diabetes_Trt	There are totally 6 levels of anti-hyperglycemia treatment defined in the MMD: 0. No treatment 1. Diet and exercise 2. One oral/non-insulin medication (metformin) 3. Two oral/non-insulin medications (metformin +

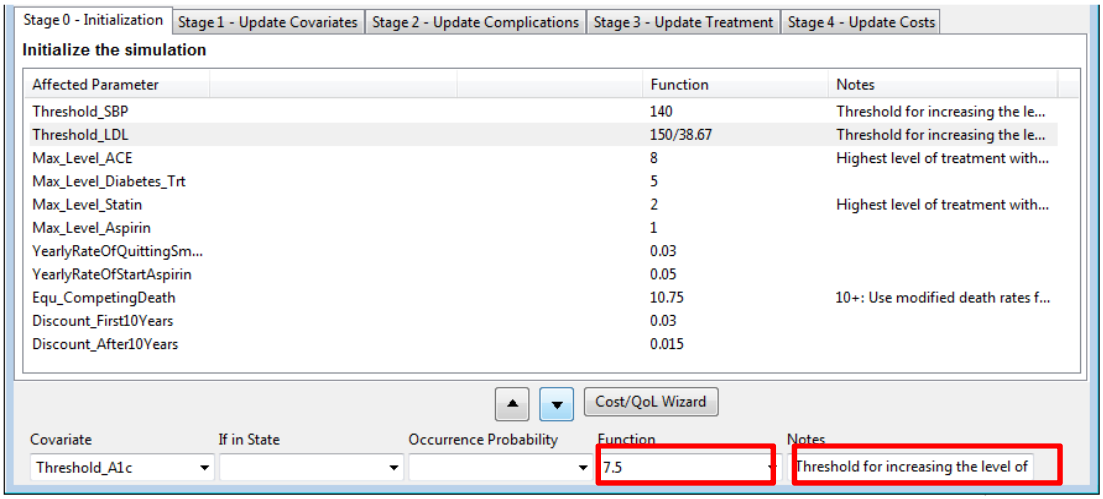
	sulfonylureas) 4. Basal insulin 5. Intensive bolus insulin You can set this parameter to any integer between 0 and 5. See Appendix A2 for the effect of or changes in different levels.
Max_Level_ACE	There are 9 levels of anti-hypertensive treatment defined in the MMD: 0. No anti-hypertensive treatment 1. one drug half dose 2. one drug full dose 3. two drugs half dose 4. two drugs full dose 5. three drugs half dose 6. three drugs full dose 7. four drugs half dose 8. four drugs full dose You can set this parameter to any integer between 0 and 8. See Appendix A2 for the effect of or change in different levels.
Max_Level_Statin	There are a totally of 2 level of anti-dyslipidemia treatment defined in the MMD: 0. No anti-dyslipidemia treatment 1. one drug half dose 2. one drug full dose You can set this parameter to any integer between 0 and 2. See Appendix A2 for the effect of or change in different levels.
YearlyRateOfQuittingSmoking	This parameter allows you to define the yearly rate of smoking cessation among current smokers who did not experience any major CVD nor was diagnosed with CAD. This parameter can be any value from 0 to 1.
YearlyRateofStartAspirin	For patients who did not experience any major CVD and were not diagnosed with CAD, you can define a compliant rate to aspirin therapy as shown in **section 4.1.2**. At the same time, not all the compliant patients start taking aspirin at the beginning. This parameter allows you to define the rate of starting aspirin among all aspirin compliant patients. This parameter can be any value from 0 to 1.

To modify the above parameters, do the following steps (using threshold for HbA1c as an example):

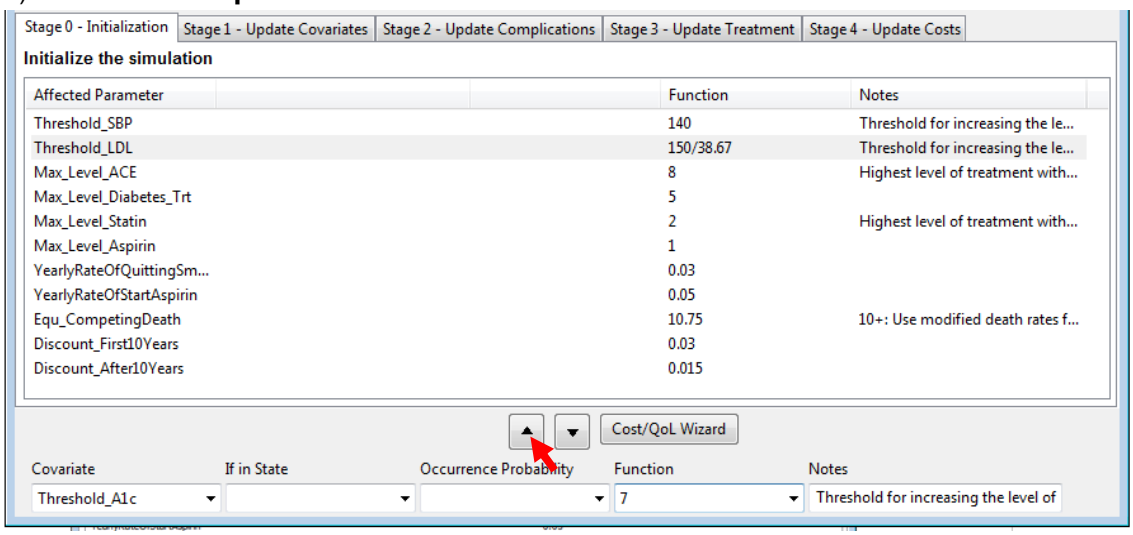
1) Highlight the parameter you would like to modify and click on the **Down Arrow** at the bottom of the window to bring down the parameter line to the editing cell.



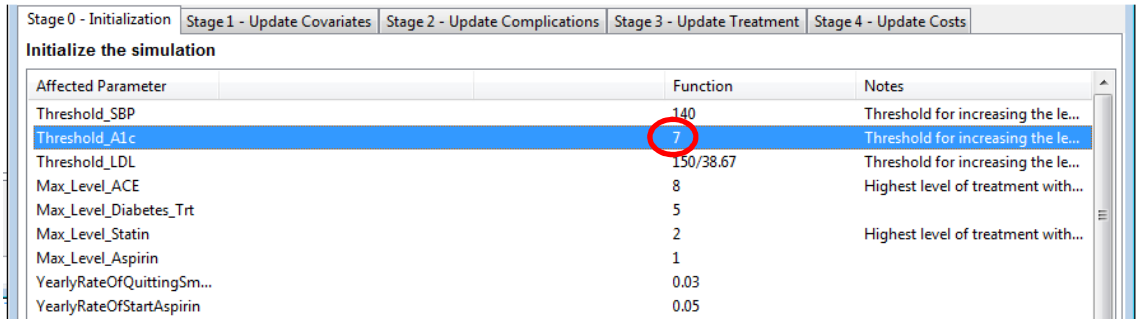
2) Change the value for this parameter in the **Function** cell. You can also modify the text in the **Notes** cell.



3) Click on the **Up Arrow.**

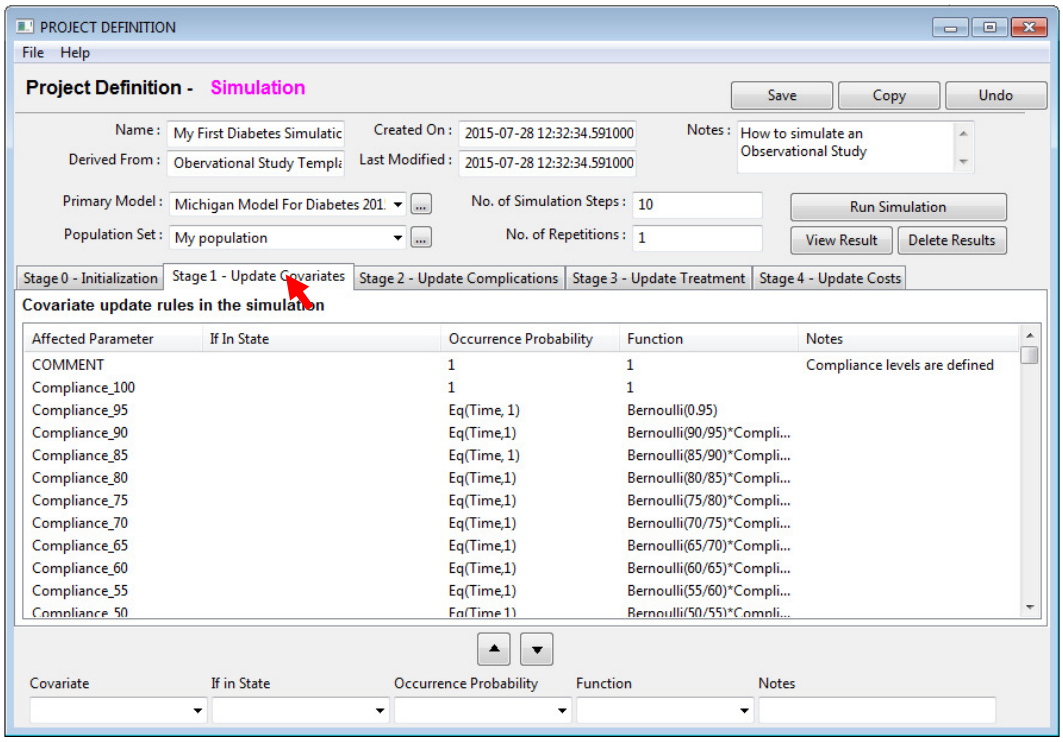


4) You should see that the parameter is back in the list of parameters with the new value.

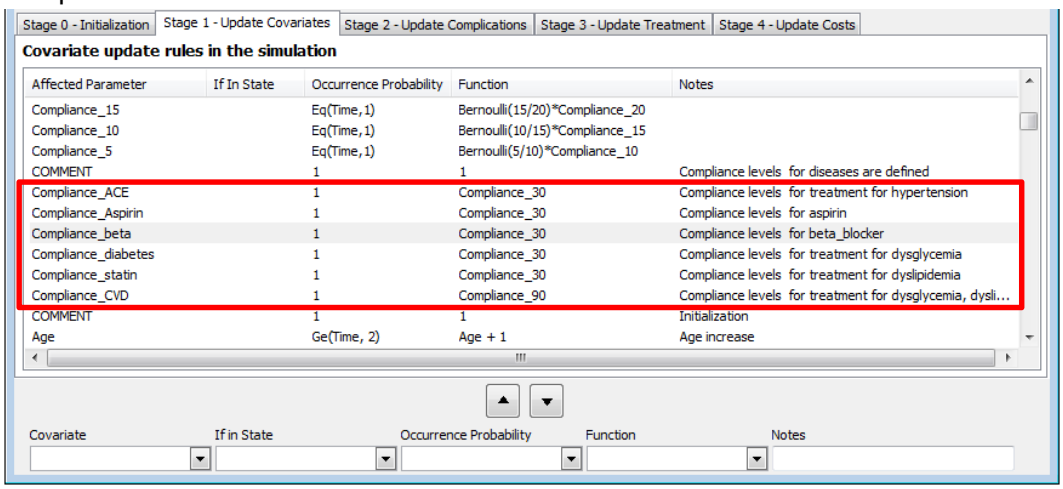


Compliance Parameters

To change/specify treatment compliance rates, click on "**Stage 1 – Update Covariates**" to bring this tag to the front.



Use the **Scrollbar** on the right to scroll down the page and find the section where the compliance levels for treatments are defined.

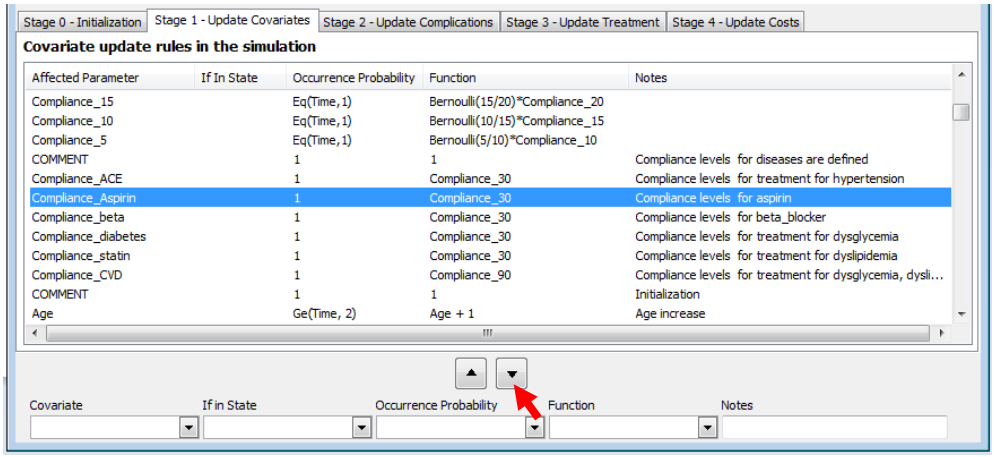


The following table shows the definition for the six compliance parameters in the model program.

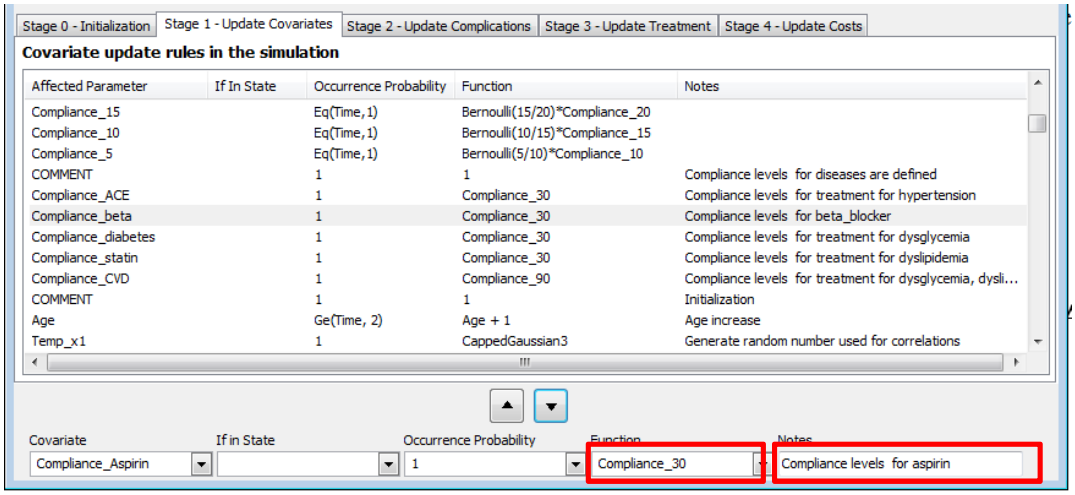
Parameter	Definition and suggested range	Function
Compliance_CVD	The proportion of patients who are willing to comply with treatment for hyperglycemia, dyslipidemia, and hypertension, and using aspirin when there is a CVD event. This number should be relatively high and higher than all the rest of the compliance parameters.	Each parameter should be set to either equal 0, or one of the following pre-set covariates: Compliance_100, Compliance_95, Compliance_90, … Compliance_10, Compliance_5. Number at the end of the name of each of the above covariates indicates the rate of compliance. For example, if you wish to set the proportion of patients that comply with treatment for hyperglycemia regardless of CVD event history to 80%, you should set Compliance_diabetes=Compliance_80.
Compliance_diabetes	The proportion of patients who comply with treatment for hyperglycemia regardless of history of CVD event.	
Compliance_ACE	The proportion of patients who comply with treatment for hypertension regardless of history of CVD event.	
Compliance_statin	The proportion of patients who comply with treatment for dyslipidemia using statin regardless of history of CVD event.	
Compliance_beta	The proportion of patients who comply with treatment using beta-blocker regardless of history of CVD event.	
Compliance_Aspirin	The proportion of patients who comply with aspirin therapy regardless of history of CVD event.	

To modify the above parameters, do the following steps (using compliance rate for aspirin as an example):

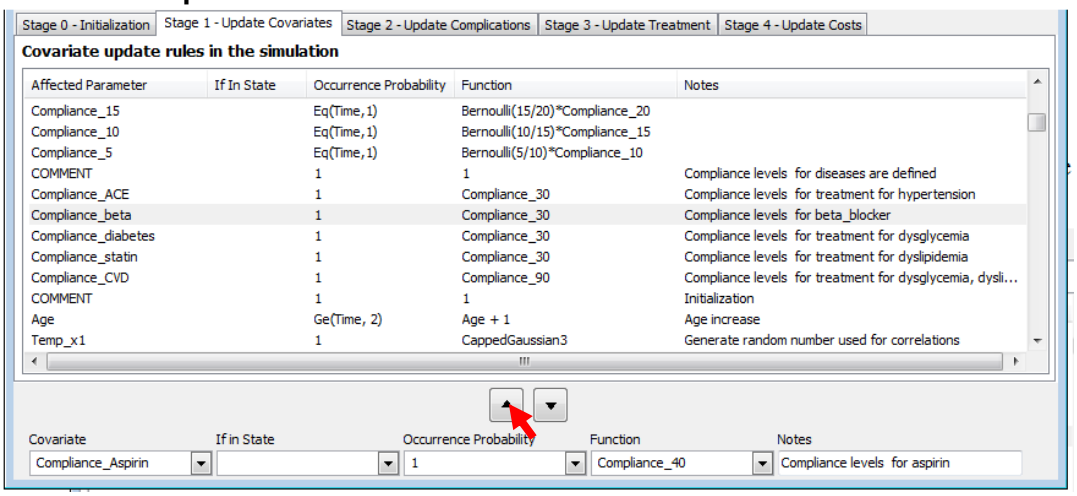
1) Highlight the parameter you would like to modify and click on the **Down Arrow** at the bottom of the window to bring down the parameter line to the editing cells.



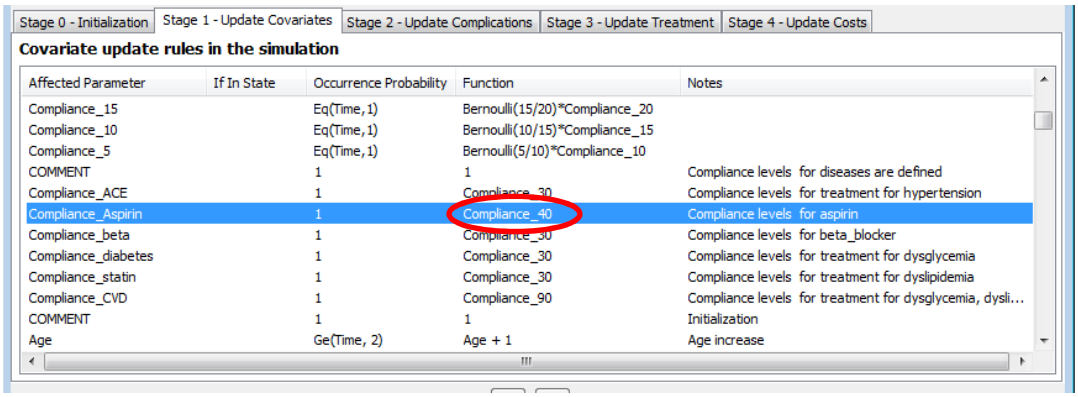
2) Change the value for this parameter in the **Function** cell. You can also modify the text in the **Notes** cell.



3) Click on the **Up Arrow.**



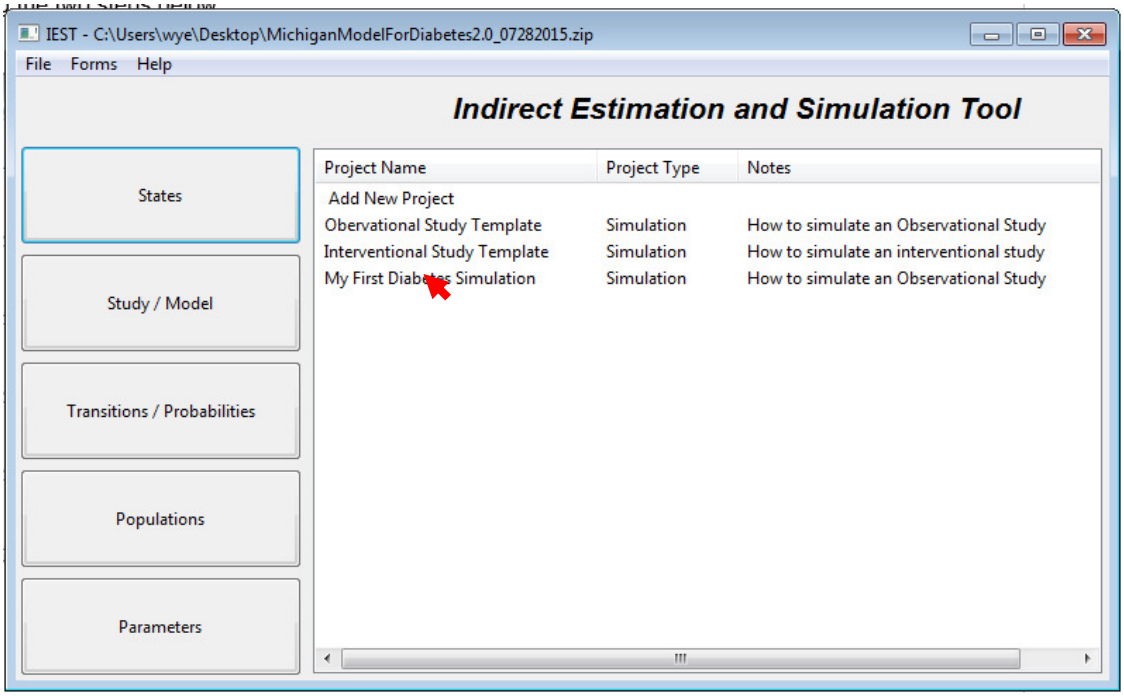
5) You should see that the parameter is back in the list of parameters above with new value.



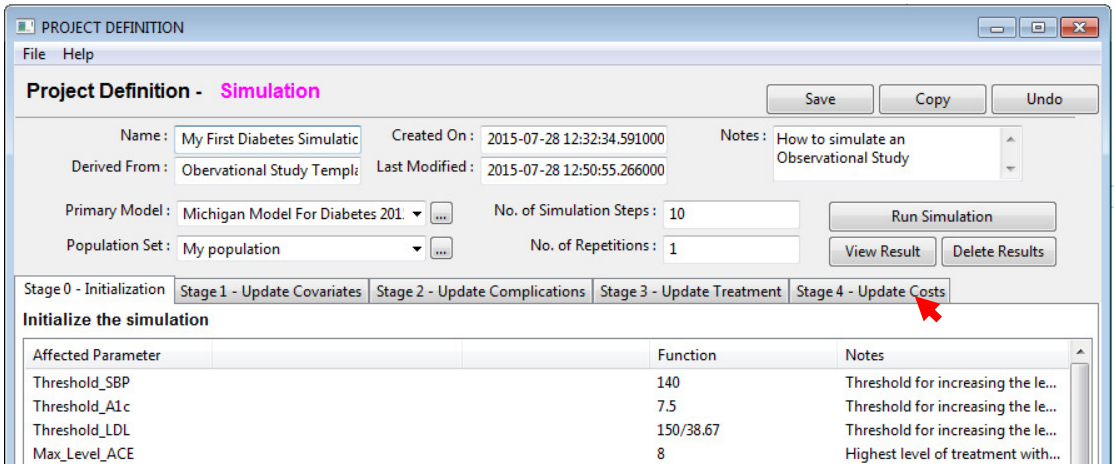
4.1.3. Defining cost values and utility scores

The MMD provides a cost module and a utility score module. To access these modules, following the two steps below.

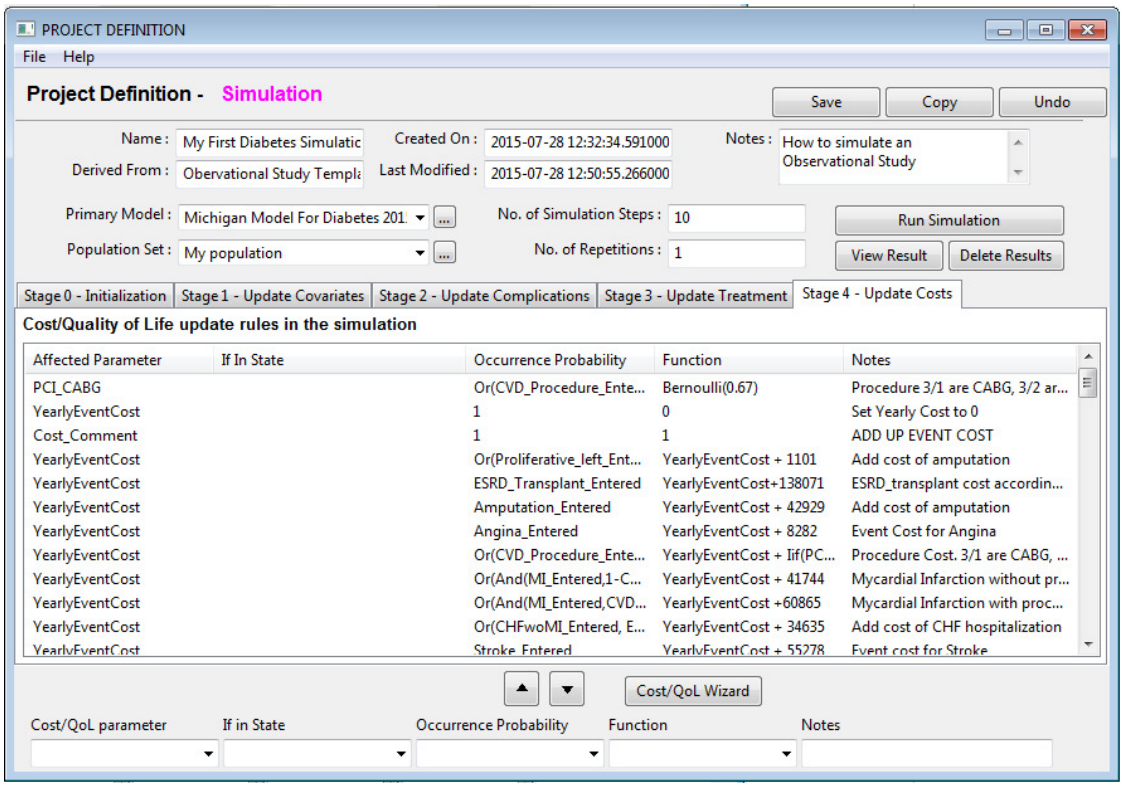
1) In the main window, click on the project name you are working on.



2) In the project window, click on the tab "**Stage 4 – Update Costs**"



On the "Update Cost" tab, you can find a series of updating rules for calculating event costs, ongoing costs, and utility values.

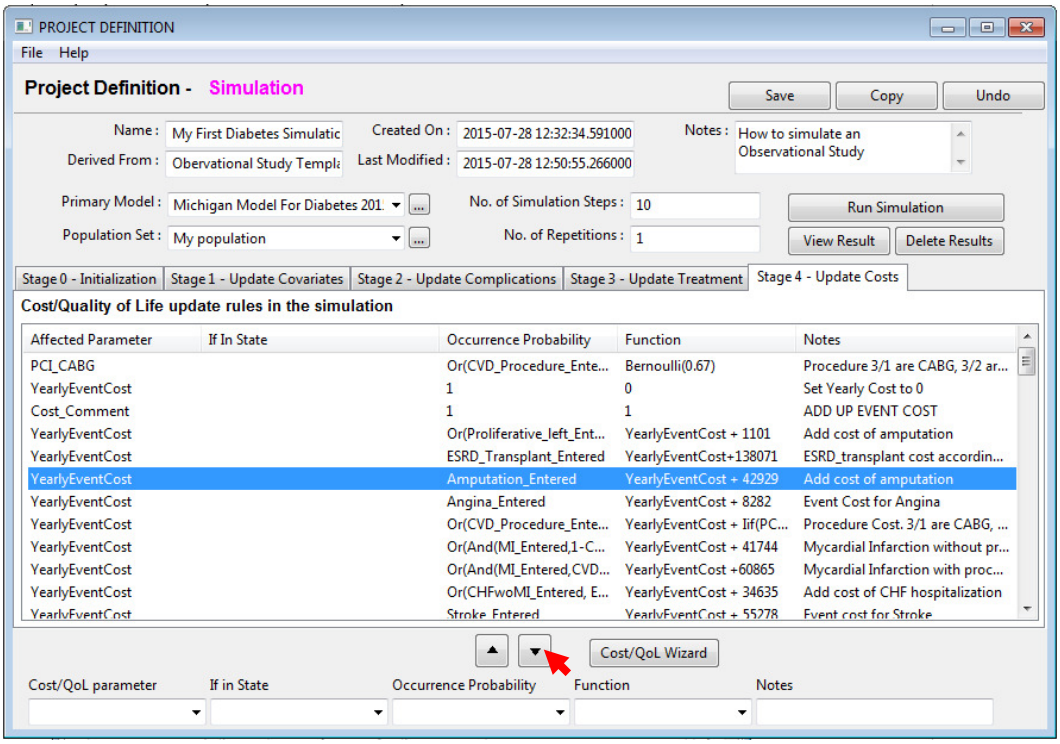


4.1.3.1. Defining cost values

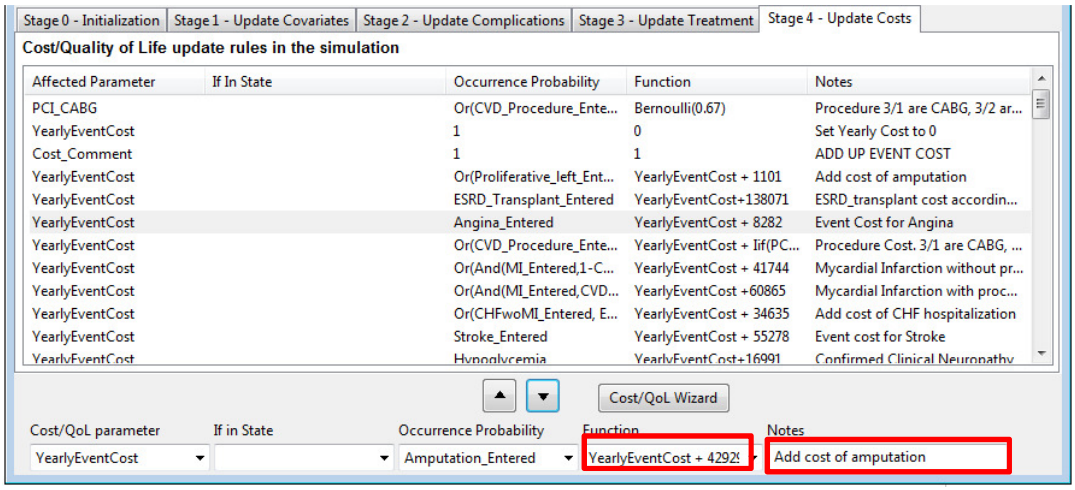
The MMD can calculate yearly and cumulative direct medical costs related to diabetes management and its complications. We divided disease-specific costs into two categories: 1) event costs that are the one-time costs and accrue within the year in which a complication first occurs, and 2) state costs that are intended to reflect the ongoing costs in subsequent years that are associated with the management of the complications. Table B1

in Appendix B shows the detailed costs of complications for MMD. All default costs are expressed in 2014 US dollars. Users can modify costs following the steps below, using the cost of amputation as an example.

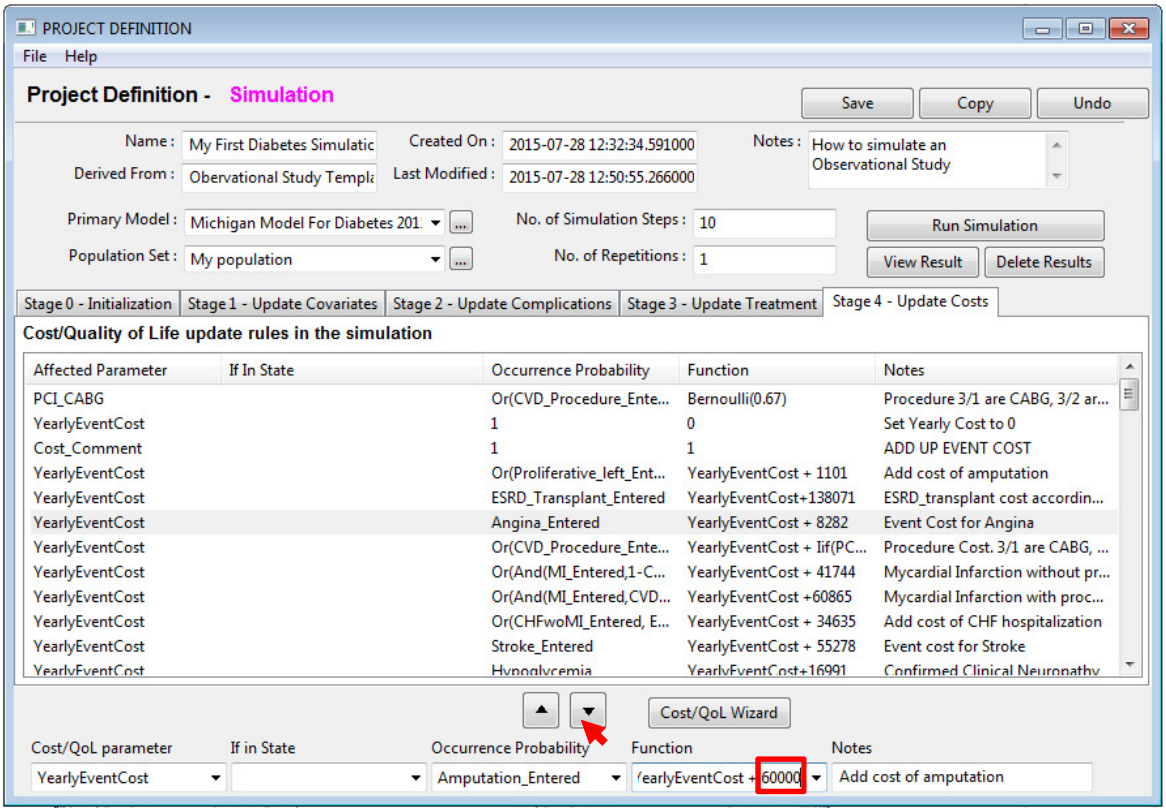
1) Highlight the cost you would like to modify and click on the **Down Arrow** at the bottom of the window to bring down the parameter line to the editing cells.



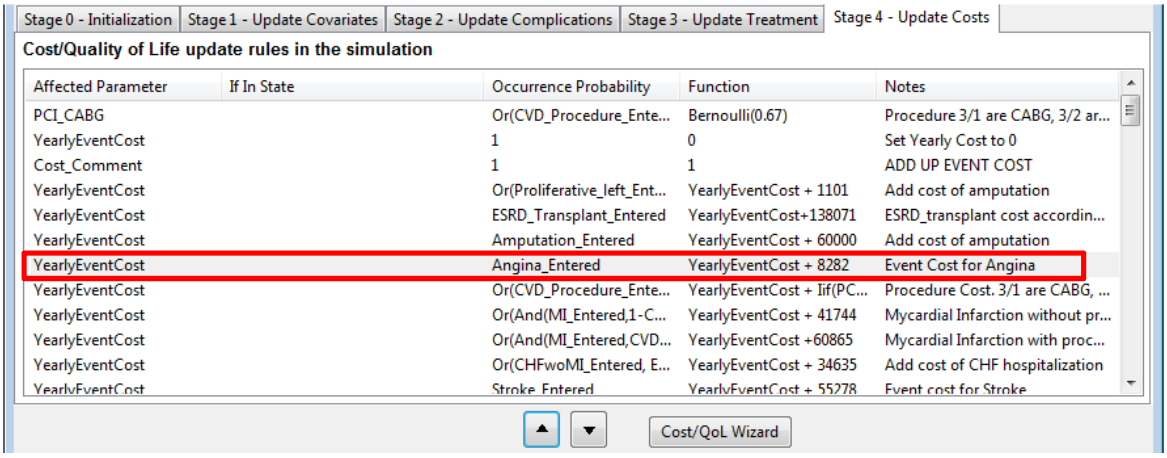
2) Change the event cost for amputation in the **Function** cell. You can also modify the text in the **Notes** cell to keep notes of this change.



3) When you are done with modifying, click on the **Up Arrow** and bring back the parameter to the cost/utility window.



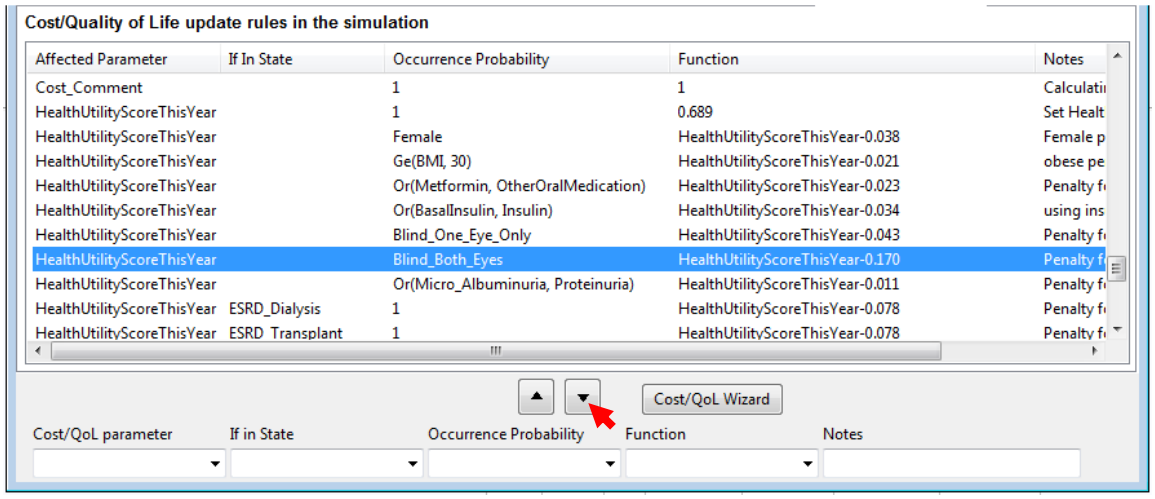
4) The modified numbers is back in the list.



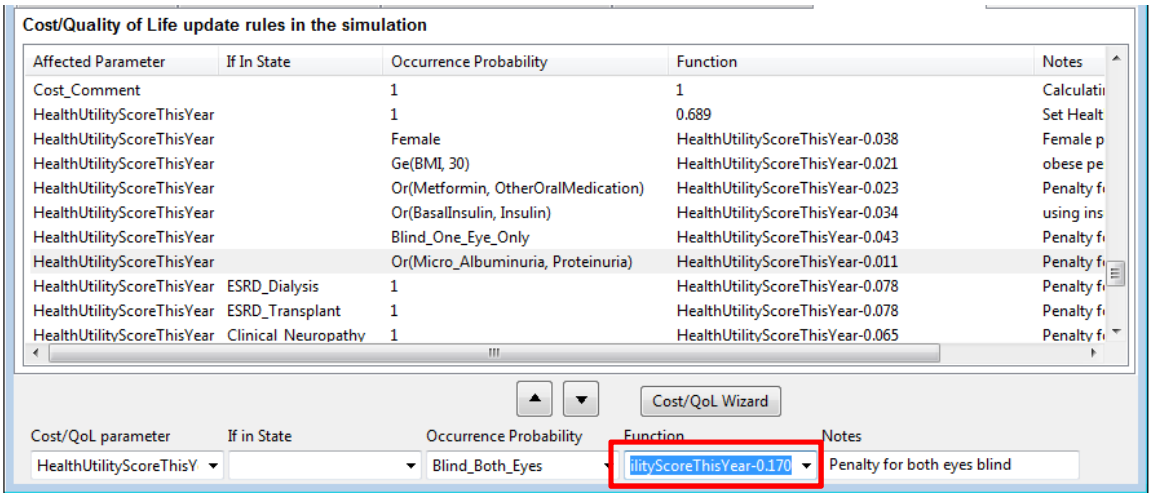
4.1.3.2. Defining utility scores

The MMD provides a utility module that can calculate yearly and cumulative values. Table C1 in Appendix C shows the utility penalties related to patient characteristics and conditions. Users can modify utility scores following the steps below, using “blind in both eyes” as an example.

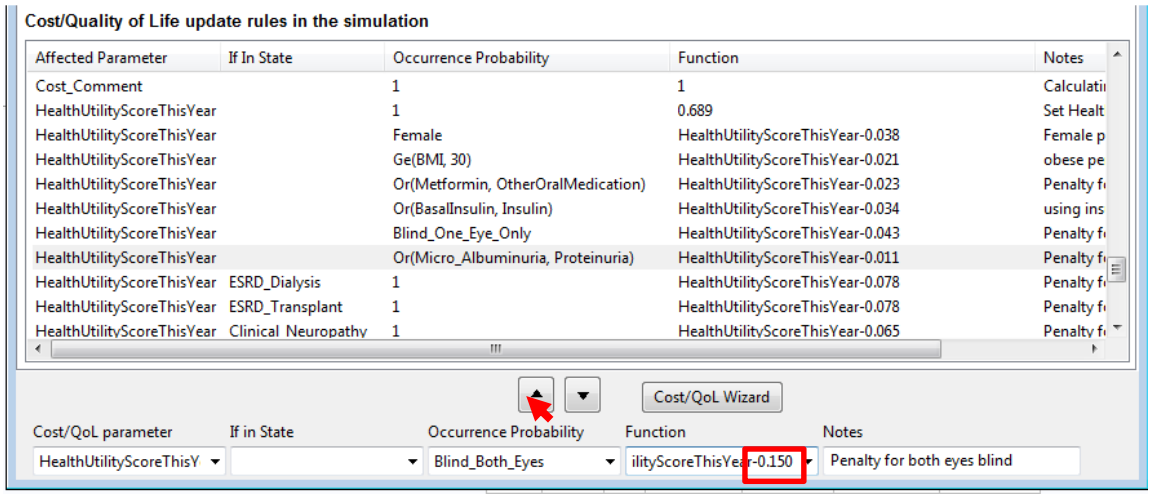
1) Highlight the utility score you would like to modify and click on the **Down Arrow** at the bottom of the window to bring down the parameter line to the editing cells.



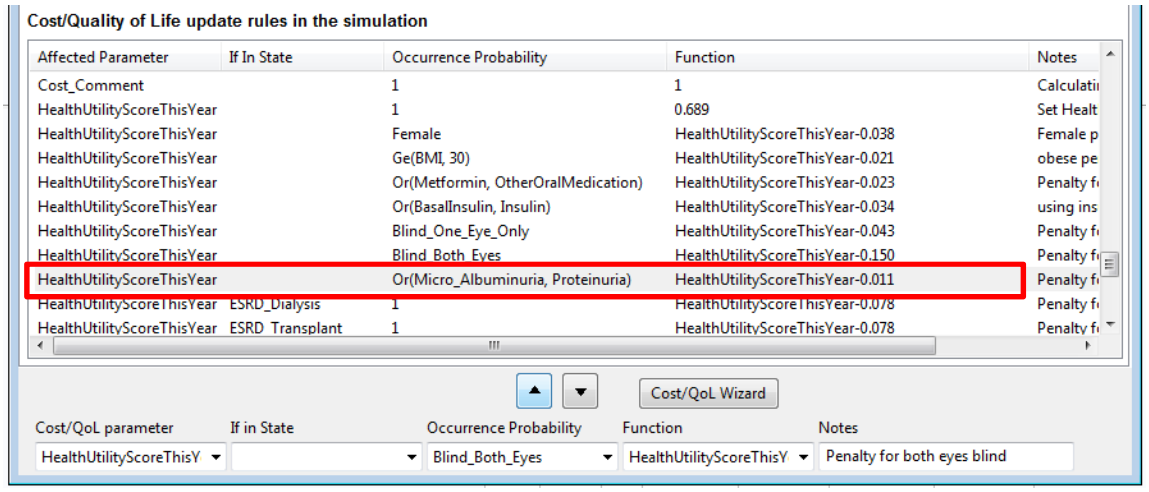
2) Change the event cost for amputation in the **Function** cell. You can also modify the text in the **Notes** cell to keep notes of this change.



3) When you are done with modifying, click on the **Up Arrow** and bring back the parameter to the cost/utility window

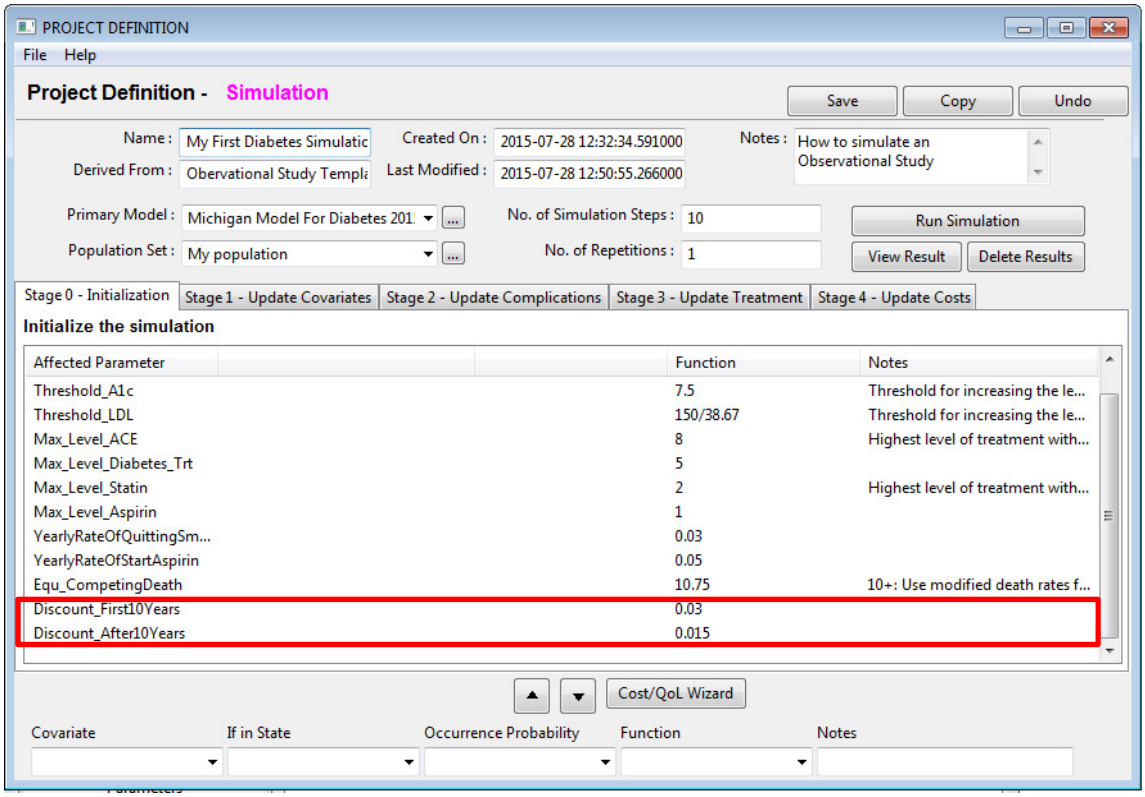


4) The modified numbers is back in the list.



4.1.3.3. Discount rates

The MMD allows the users to set the annual discount rate to be applied to life expectancy, quality-adjusted life expectancy, and medical cost estimates. Two different discount rates can be applied, for example, a discount rate of 0.03 (3%) can be specified for the first 10 years and then 0.015 (1.5%) for all subsequent years. If discounting is not required, enter “0”. To modify the discount rates, click on the **Stage 0 - Initialization** tab and use the **Down Arrow** and **Up Arrow** at the bottom of the tab.



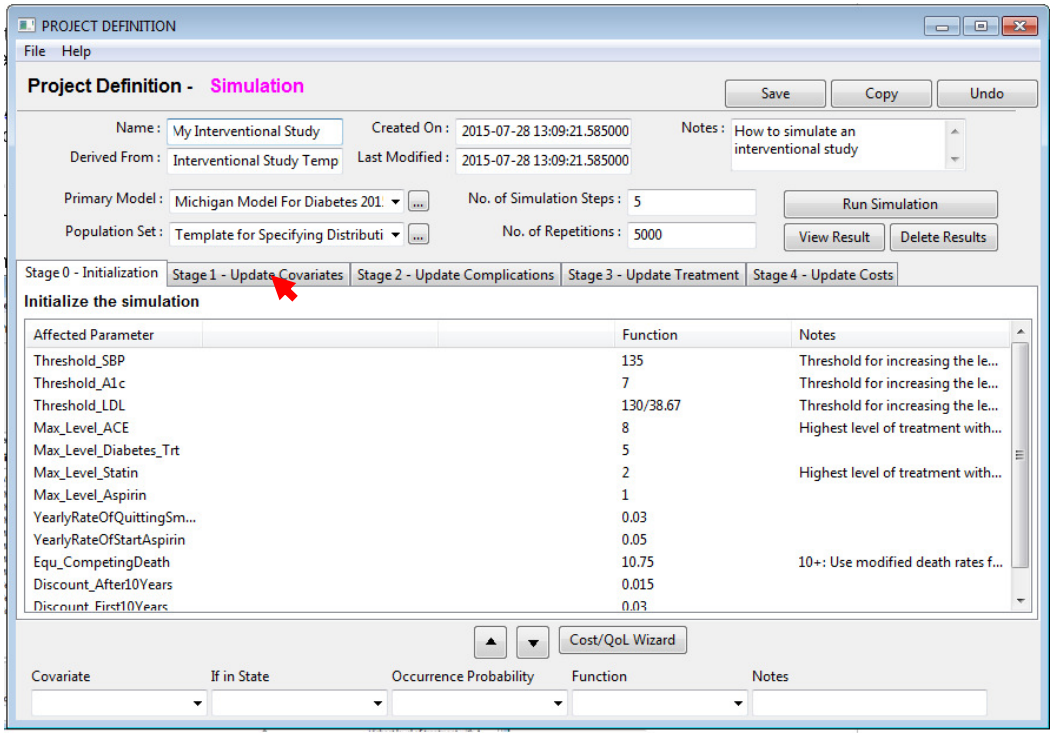
4.1.4. Defining the first year treatment parameters when simulating an intervention study

When setting up a simulation, the most important difference between an observational study and an interventional study is how to set up the first year. In an observational study, the transition probabilities for disease progression are calculated based on the baseline parameters. In contrast, in an interventional study, since patients receive an intervention right after they are enrolled in the study, risk factors often change largely after they started due to changes in treatment. Therefore when setting up an interventional study, in the first year of the simulation, MMD allows user to model the change of treatments, which consequently changes the risk factor levels, before calculating transition probabilities.

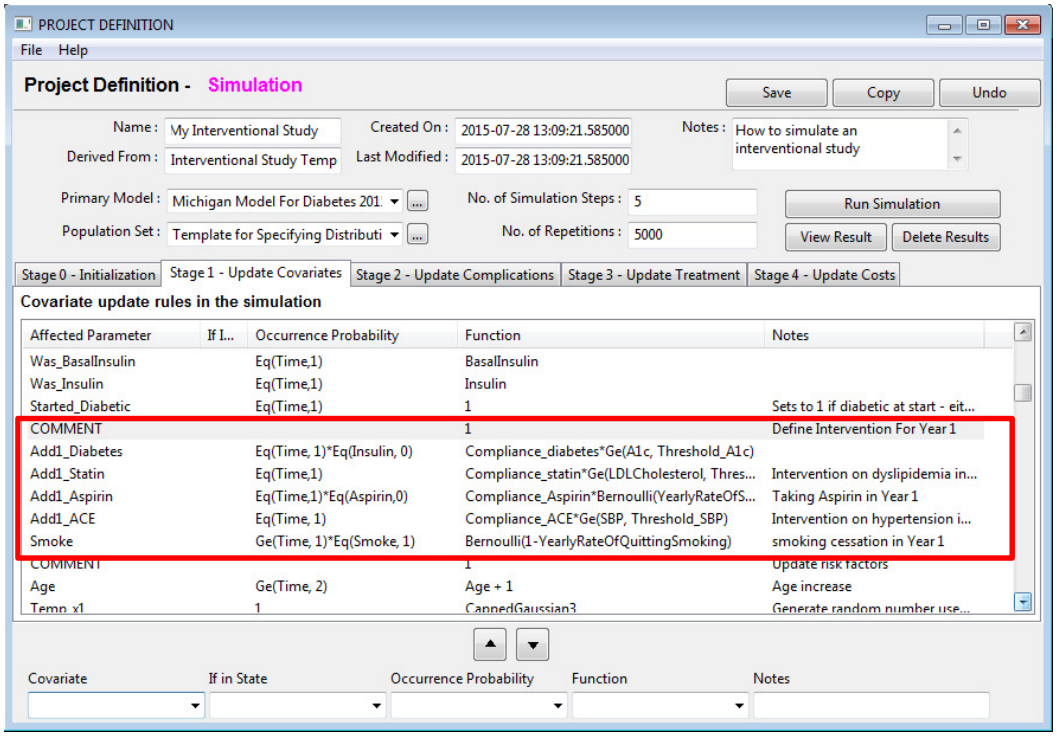
In the default model, the first year changes follow the same rule as other years. For example, if the treatment threshold for hyperglycemia is set to be 6.5, a patient whose HbA1c value is larger than 6.5 at baseline will receive treatment enhancement right after the simulation starts. Their HbA1c and weight values will change accordingly. To modify the rules for the first year risk factors and treatment changes, do the following steps.

1) Follow instruction in 4.1.1 to set up your own simulation project by copying ‘Interventional Study Template’.

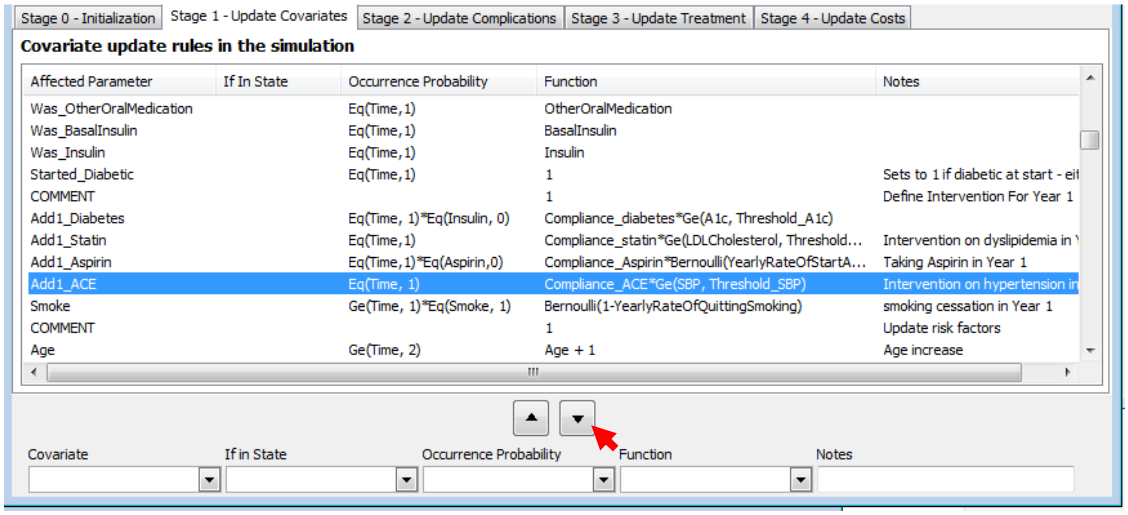
2) On the **Project Definition** window, click on the tab **Stage1-Update Covariates.**



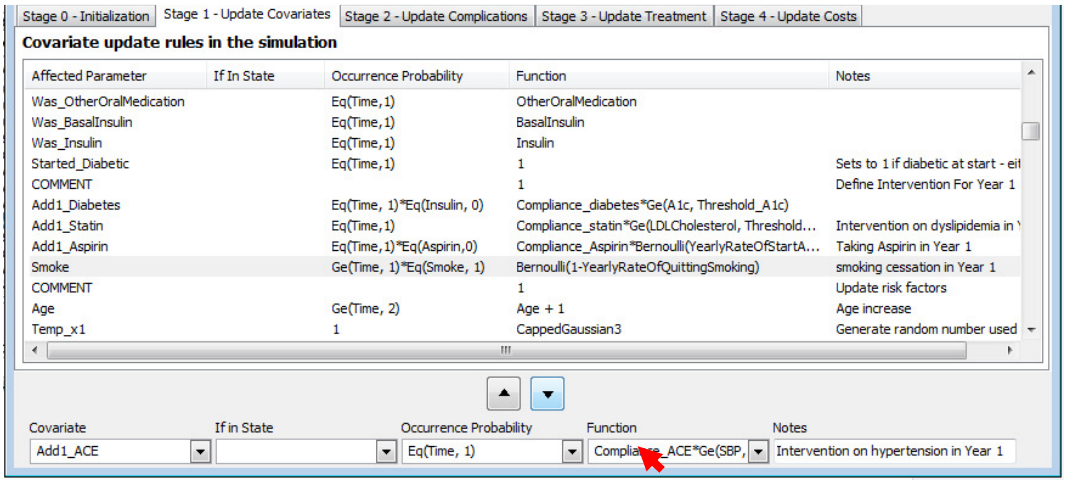
3) Scroll down on this tab, you can find the section for defining treatment changes at the beginning of Year 1.



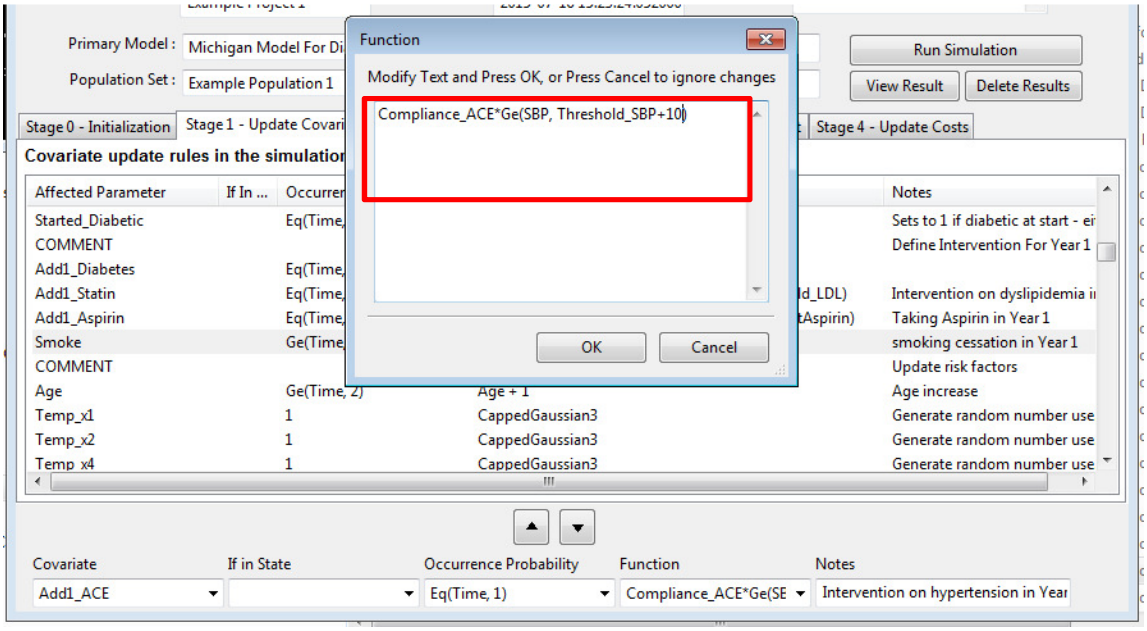
4) To modify the treatment changing rules in year 1, highlight the treatment you would like to modify and click on the **Down Arrow** at the bottom of the window to bring down the parameter line to the editing cells.



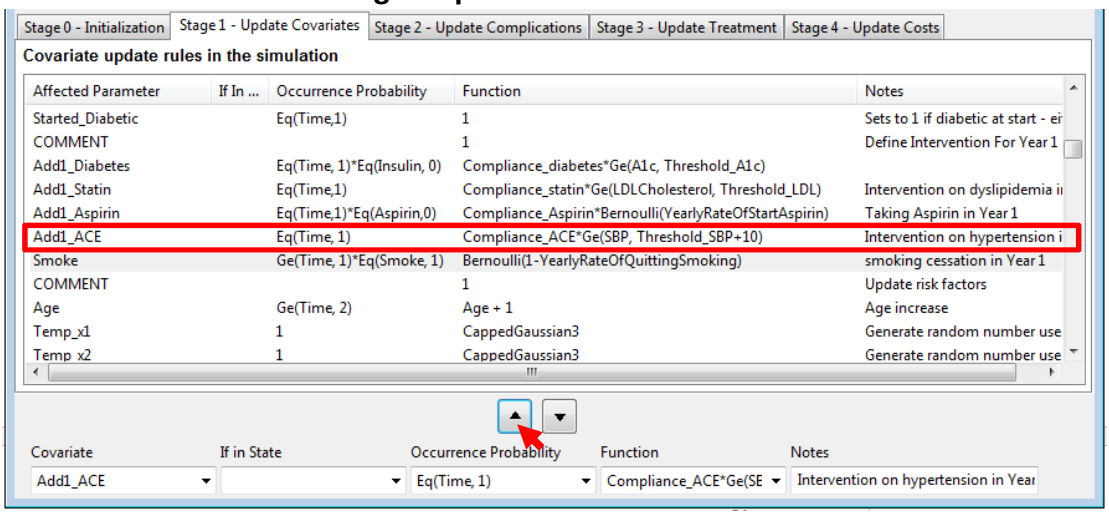
5) Double click the function window to open a larger editing window



6) You now can modify the function in the editing window. For example, below we modify the function so that the treatment threshold for hypertension at baseline is 10 units higher than the usual treatment threshold.



7) Close the editing window by clicking **OK**, and then click on the **Up Arrow** to bring the modified line back to the **Stage1-Update Covariate** tab window.



Treatment changes not only happen to subjects enrolled in an active treatment arm, but also mostly happen to subjects enrolled in placebo arms as well. When simulating disease progression for subjects in a placebo arm of an interventional study, one should not use the template for an observational study to simulate a placebo arm in an interventional study.

4.2. Modifying the default MMD (For advanced users only)

If your project needs additional changes which was not mentioned in the instructions above, please contact us at help.MichiganModelForDiabetes@umich.edu.

5. Entering Population Information

Populations can either be inputted as data (to be used in a Simulation or an Estimation), or set by specifying a distribution (to be used in Estimation or for randomly generating population sets). It is the responsibility of the users of MMD to ensure that only valid values are entered as the software applies a few data entry checks. The items needed for each subject are listed in the following table:

Variable Name	Definition		Legal Range
System Variables			
Diabetes_Type_2	State indicator for having type 2 diabetes		1=Yes
Alive	State indicator for being alive		1=Yes
Demographics Characteristics			
Age	Current age in years		[1,100]
Duration_Of_Diabetes	Duration in years since diagnosis of diabetes		≤ Age
Male	Gender variable		0=Female; 1=Male
Race	Race		1=White 2=Black
BMI	Weight/Height^2 (Weight in kilograms [1.0 kg=2.2 pounds] Height in meters [1.0 meter=39 inches])		[10, 50]
Height	Height in meters [1.0 meter=39 inches]		[0, 2.5]
Current Risk Factors			
SBP	Systolic blood pressure (mmHg)		[60, 280]
DBP	Diastolic blood pressure (mmHg)		[20, 140]
Smoke	Smoking status		0=Non-smoker; 1=Smoker
HDLCholesterol	High-density lipoprotein cholesterol in mmol/L [1 mmol/L=38.6mg/dl]		[0.3, 5]
LDLCholesterol	Low-density lipoprotein cholesterol in mmol/L [1 mmol/L=38.6mg/dl]		[0.3, 11]
Triglycerides	Triglycerides in mmol/L [1 mmol/L=38.6mg/dl]		[0, 20]
TotalCholesterol	Total Cholesterol in mmol/L [1 mmol/L=38.6mg/dl]		[0.6, 25.12]
HbA1c	Hemoglobin A1c (%)		[0, 20]
AF	Atrial fibrillation		1=Yes; 0=No
Disease Status (Within each sub-model defined below, one and only one variable should be set to one)			
No_Cerebrovascular_ Disease	No cerebrovascular disease	Cerebrovascular disease sub-model	1=Yes; 0=No
Survive_Stroke	Alive with stroke history		1=Yes; 0=No
No_CVD	No history of coronary heart	Coronary heart disease sub-model	1=Yes; 0=No

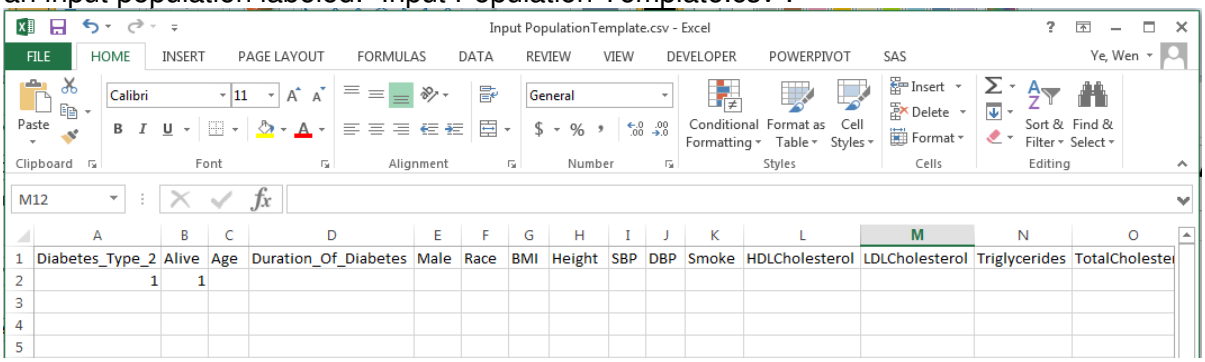
	disease		
Angina[¥]	Coronary artery disease without history of MI or heart failure		1=Yes; 0=No
CHFwoMI	History of heart failure but not MI		1=Yes; 0=No
CADwProc	History of revascularization procedure with no history of MI		1=Yes; 0=No
Survive_MI	History of MI (can be more than once) with no history of heart failure		1=Yes; 0=No
CHF[§]	History of heart failure and history of MI		1=Yes; 0=No
No_Nephropathy	No nephropathy	Nephropathy sub-model	1=Yes; 0=No
Micro_Albuminuria	Microalbuminuria is defined as 30 mg/g ≤ ACR < 300 mg/g		1=Yes; 0=No
Proteinuria	ACR ≥ 300 mg/g		1=Yes; 0=No
ESRD_Dialysis	End stage renal disease with need of dialysis but no history of transplant		1=Yes; 0=No
ESRD_Transplant	End stage renal disease with history of transplant		1=Yes; 0=No
No_Neuropathy	No neuropathy	Neuropathy sub-model	1=Yes; 0=No
Clinical_Neuropathy	Distal symmetric (sensory) neuropathy		1=Yes; 0=No
Amputation	History of amputation due to diabetic neuropathy		1=Yes; 0=No
No_Proliferative_Retinopathy_left	Normal left eye	Left eye retinopathy sub-model	1=Yes; 0=No
Nonproliferative_left	Left eye has non-proliferative retinopathy		1=Yes; 0=No
Proliferative_left	Left eye has		1=Yes; 0=No

	proliferative retinopathy		
Blind_Eye_left	Left eye is blind		1=Yes; 0=No
No_Proliferative_Retinopathy_right	Normal right eye	Right eye retinopathy sub-model	1=Yes; 0=No
Nonproliferative_right	Right eye has non-proliferative retinopathy		1=Yes; 0=No
Proliferative_right	Right eye has proliferative retinopathy		1=Yes; 0=No
Blind_Eye_right	Right eye is blind		1=Yes; 0=No
No_Macular_edema_left	Left eye does not have macular edema	Left eye retinopathy sub-model; If left eye is blind, both variables should be set to be 0.	1=Yes; 0=No
Macular_edema_left	Left eye has macular edema		1=Yes; 0=No
No_Macular_edema_right	Right eye does not have macular edema	Right eye retinopathy sub-model; If right eye is blind, both variables should be set to be 0.	1=Yes; 0=No
Macular_edema_right	Right eye has macular edema		1=Yes; 0=No
Medication			
IntensiveLifeStyle	Diet and exercise	There are five stages for anti-hyperglycemia treatment in MMD. These five stages are mutually exclusive of each other. At most, only one of them can be set to 1, and the rest of them need to be set to zero. If a subject is on both insulin and metformin, s/he should be considered as at the 5th stage treatment for hyperglycemia, and therefore only the variable Insulin is set to be 1[a].	1=Yes; 0=No
Metformin	Metformin		1=Yes; 0=No
OtherOralMedication	Two or more oral/non-insulin medications (e.g., metformin + sulfonylureas)		1=Yes; 0=No
BasalInsulin	Basal insulin		1=Yes; 0=No
Insulin	Intensive bolus insulin		1=Yes; 0=No
Beta_Blocker	Whether a subject is taking beta-blocker		1=Yes; 0=No
Ace_Inhibitor	Whether a subject is taking any hypertension medication that is no beta-blocker		1=Yes; 0=No
Statin	Whether a subject is taking any medication for dyslipidemia		1=Yes; 0=No
Aspirin	Whether a subject is taking aspirin		1=Yes; 0=No

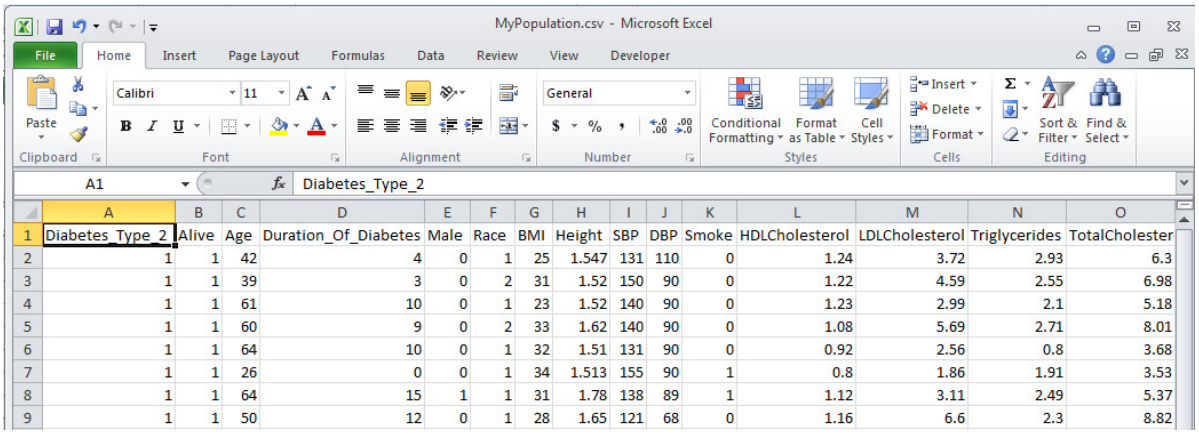
[¥]This variable is an indicator for the state "CAD w/o MI" as in shown in Appendix A. For historical reason this variable name for this state was name as Angina in the software.
[§] This variable is an indicator for the state "CHF after MI" as in shown in Appendix A. For historical reason this variable name for this state was name as CHF in the software.
[a]Additional instructions to set up five variables of medications for anti-hyperglycemia treatment: 1) If a subject is on insulin therapy in which only basal insulin or only premixed insulin is used, s/he should be considered at the 4th stage treatment for hyperglycemia, and therefore only the variable BasalInsulin is set to be 1. 2) If a subject is on insulin therapy in which any of rapid-acting insulin, short-acting insulin, or intermediate-acting insulin is used, s/he should be considered at the 5th stage treatment for hyperglycemia, and therefore only the variable Insulin is set to be 1.

5.1 Input as data

In the download folder, the users can find an Excel file that provides a template for creating an input population labeled: "Input Population Template.csv".

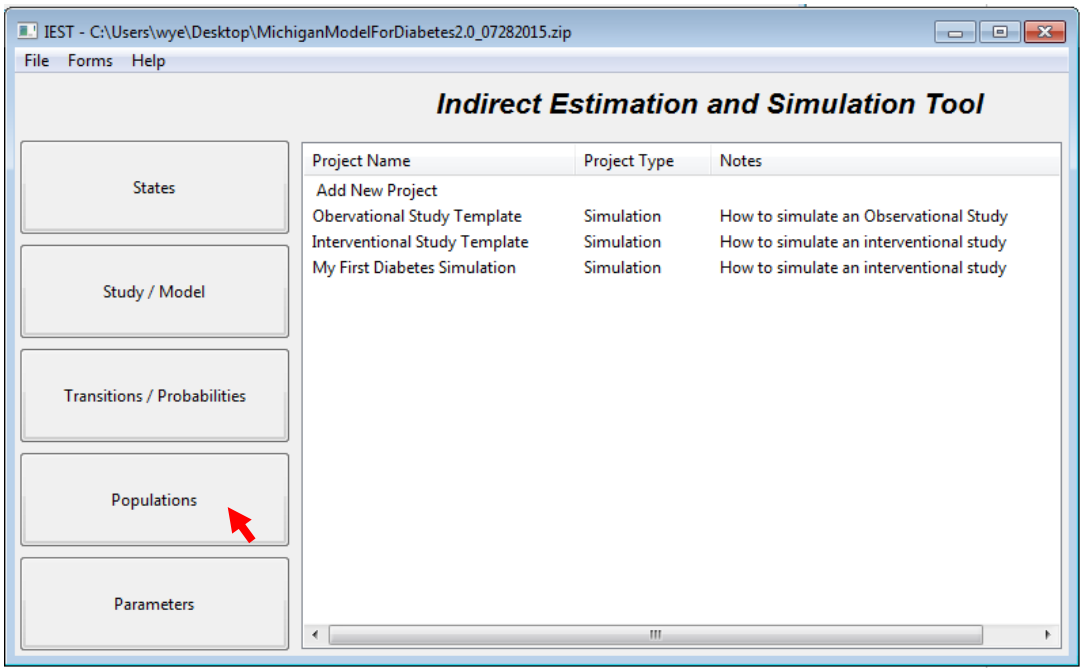


The current version of the IEST software does not accept missing values. When the data is ready, save the file as a .csv file and change the file name.

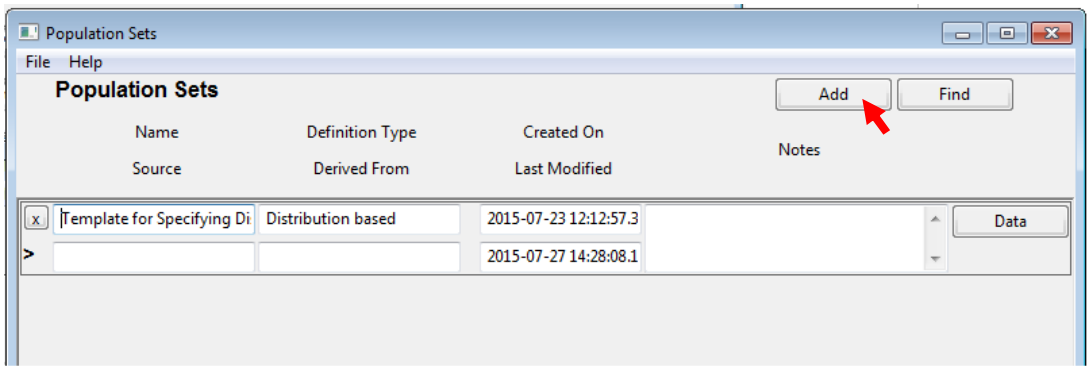


To read in the population data, do the following steps.

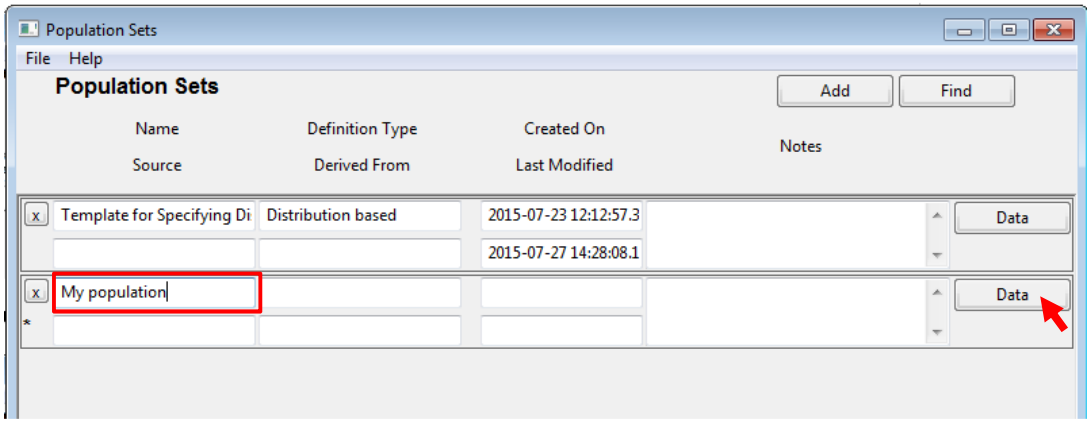
1) Click on the "**Populations**" button on the left side of the main window to open the population sets window. If you have your Project Definition window open, you need to first close it to have access to the main window.



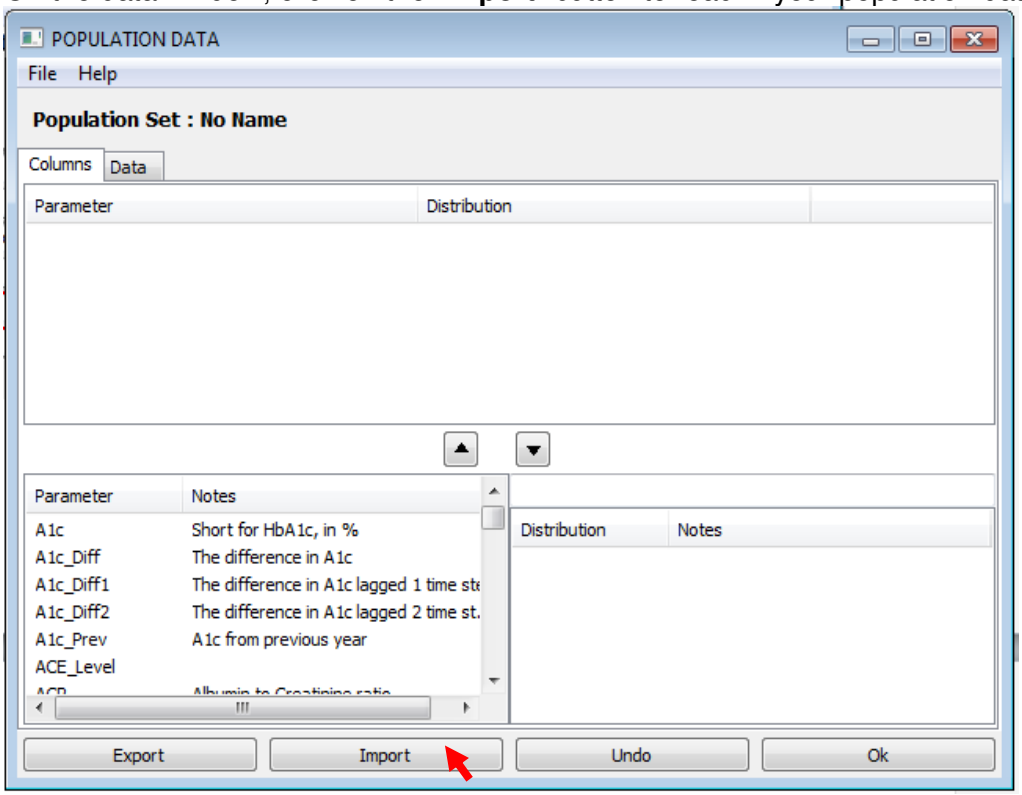
2) Click the "**Add**" button on the Population Sets window to start creating a new population set.



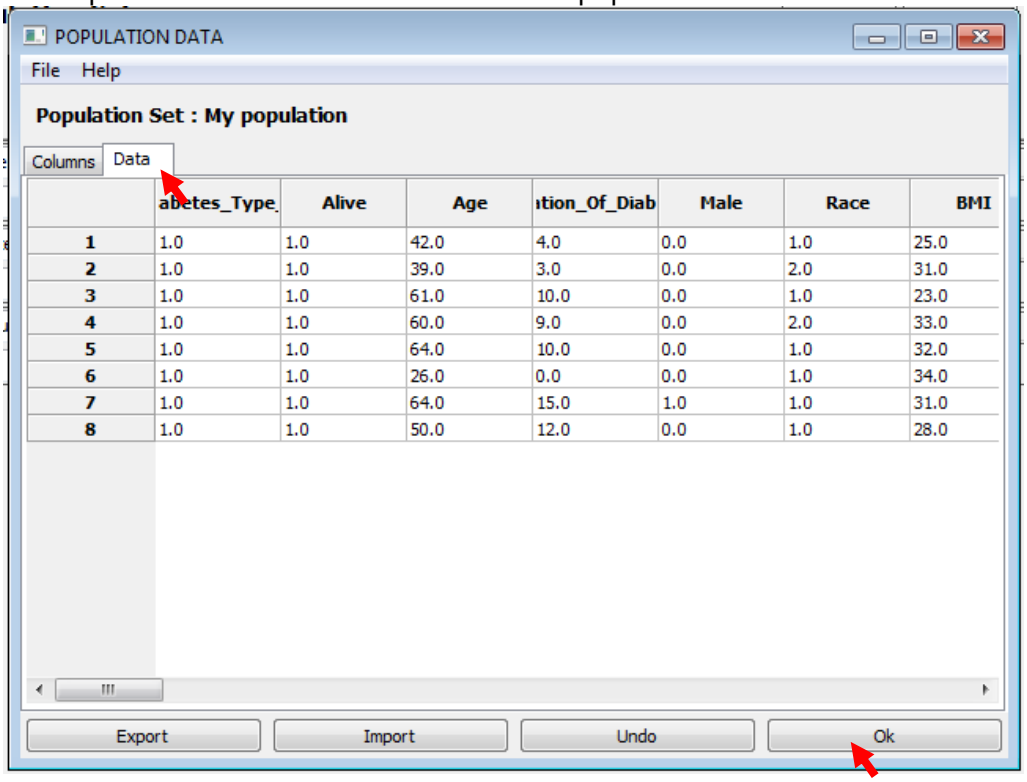
3) Name your population data and click on the "**Data**" button on the right to open the data window.



4) On the data window, click on the "**Import**" button to read in your population data set.



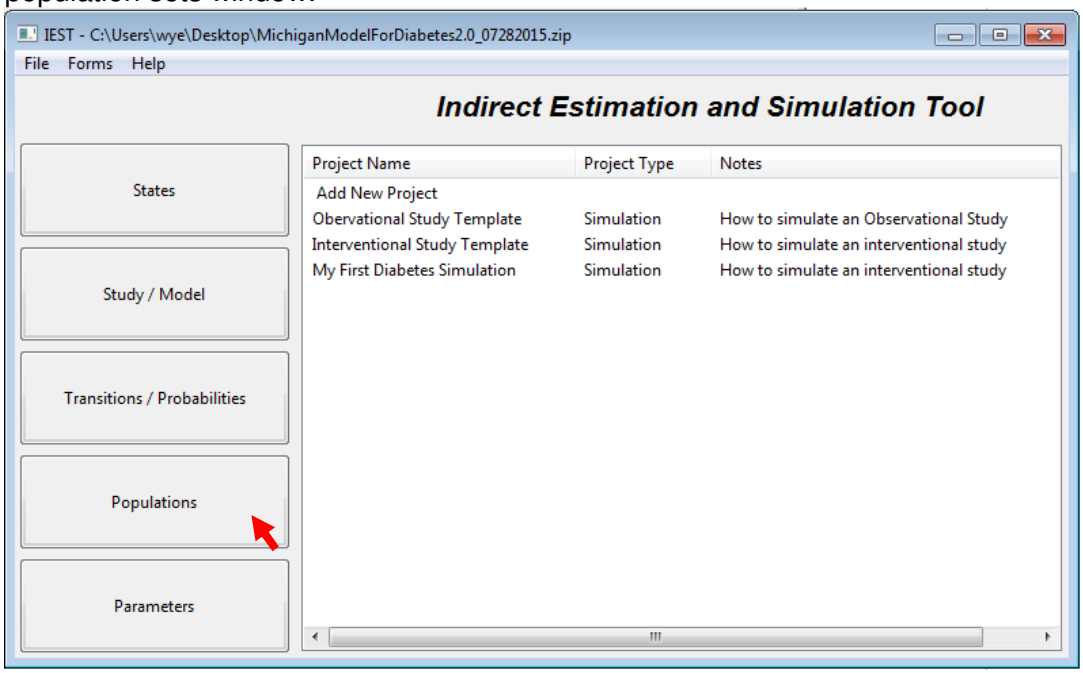
5) If the data is successfully read in, you can see it on the "**Data**" tab. Click "**OK**" and close the Population Sets window to save the this population set.



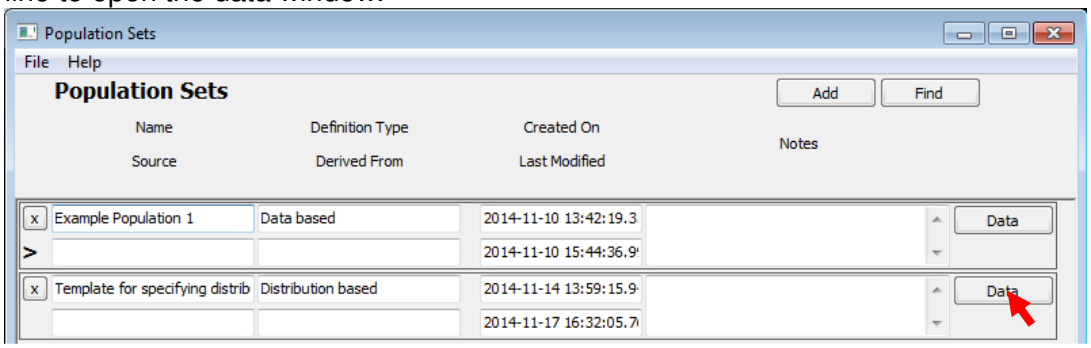
5.2 Specify a distribution

An alternative to inputting a data set with individual information is to simulate a baseline population using population level summary statistics. To do so you can use the template for specifying a distribution that we included in the default MMD.

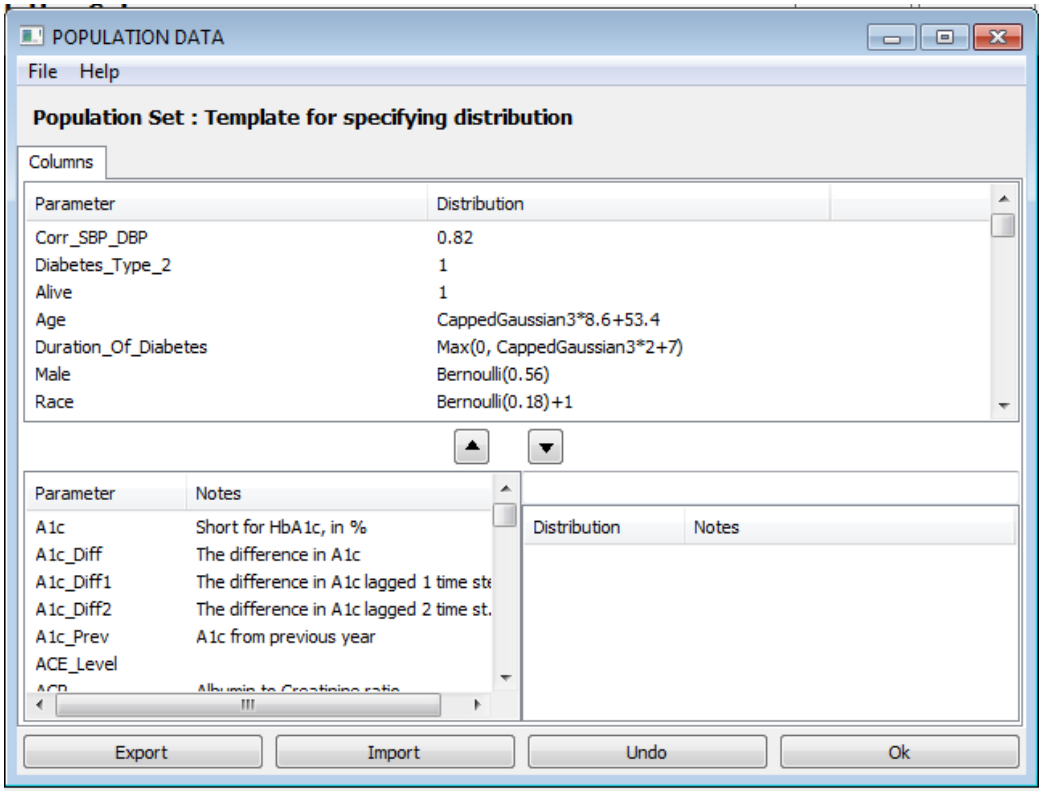
1) Click on the "**Populations**" button on the left side of the main form to open the population sets window.



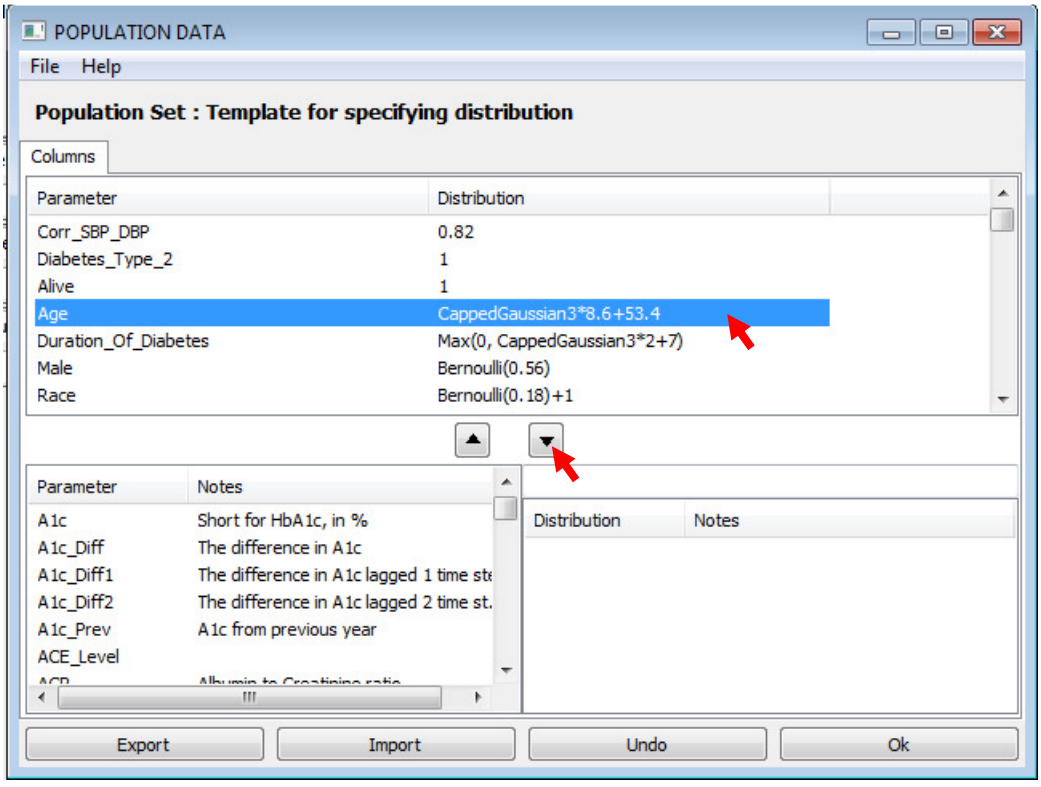
2) Click on the "**Data**" button on the right side of the "Template for specifying distribution" line to open the data window.



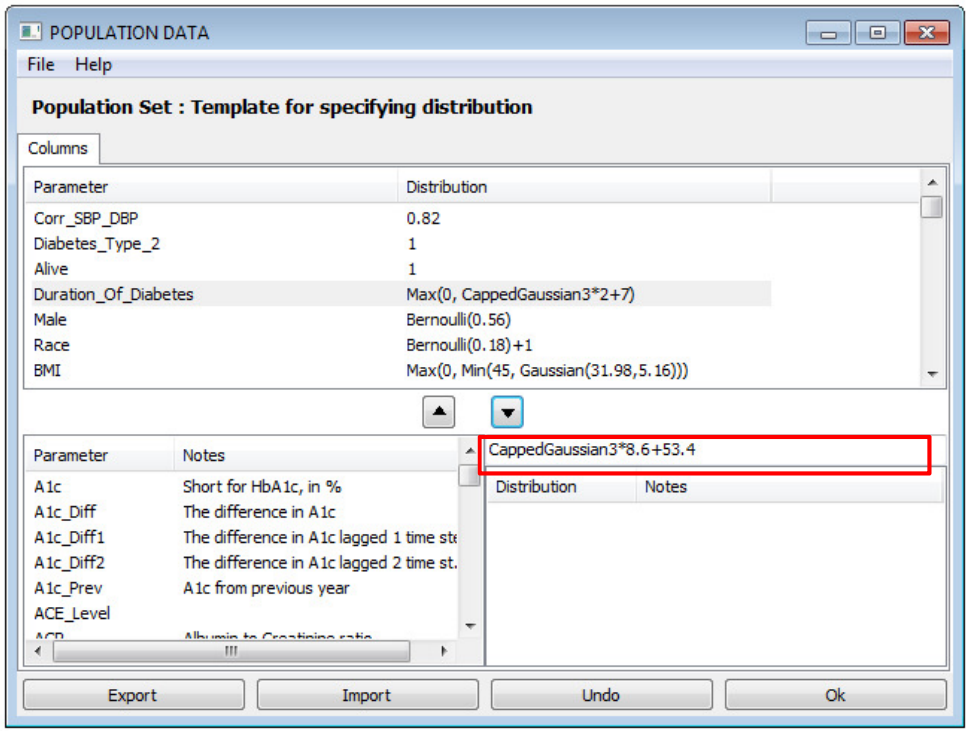
In the following data window, you can see a list of distributions for all the required variables as listed in the table in **Section 5** (page 32-35). You can change the definition for any of these variables to suit your population. You may use different type of expressions and functions to define you population. See **Appendix D** for a list of Python expressions that are allowed in the IEST software. It is important to keep the order of how these distributions are defined.



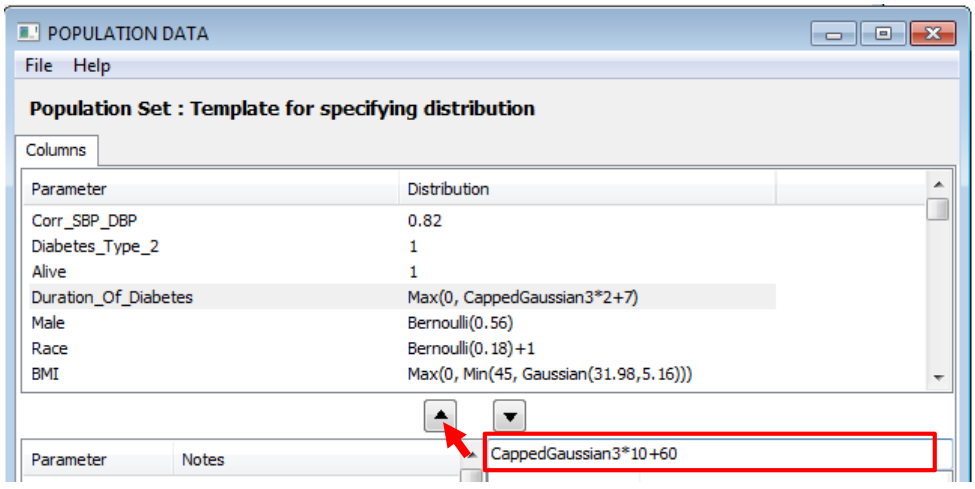
3) Below we use the "Age" variable as an example to show you how to modify the distribution. Click and highlight the line of the variable you would like to modify and click the **Down Arrow**" button.



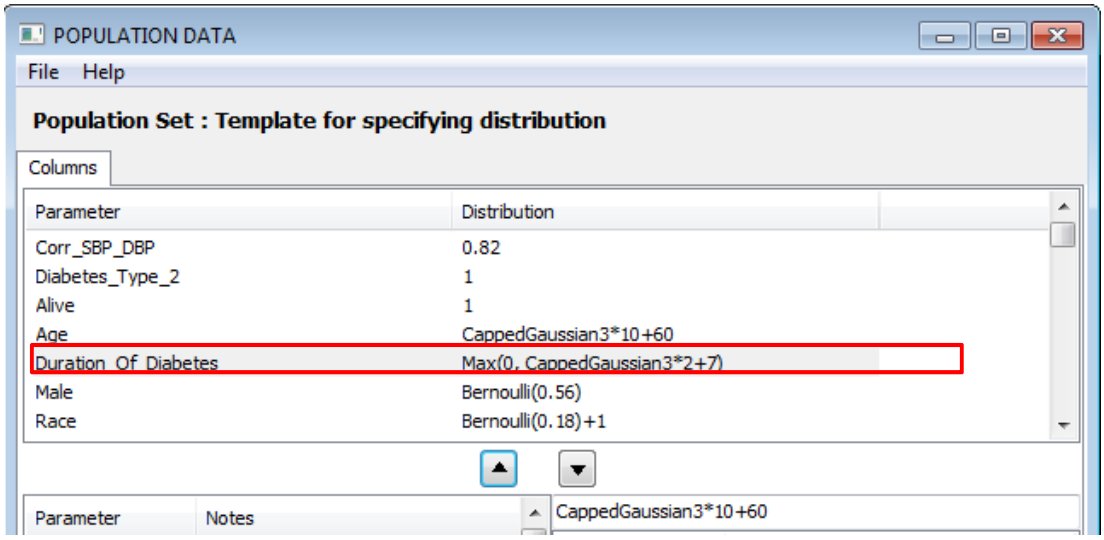
4) The original distribution for the variable age disappears from the top list and appears in the narrow window in the middle. CappedGaussian3 is a system function that generates a standard normal random number with all numbers < -3 or > 3 truncated (i.e. any randomly drawn numbers < -3 are set to be -3; any randomly drawn numbers > 3 are set to be 3). 8.6 is the standard deviation and 53.4 is the mean for the normal distributed age variable in the template. We use CappedGaussian instead of the standard normal random number to avoid extreme values.



5) Type in the narrow window to modify the distribution, and click the **Up Arrow** button to send the distribution definition for “Age’ back to the upper list.



6) The updated list looks like this:



The following table explains how the template distribution is set up to help the users understand how to set up and modify these distributions.

Variable Name	Coding in Template	Comments
System Variables		
Corr_SBP_DBP	0.82	
Diabetes_Type_2	1	Do not change
Alive	1	Do not change
Demographics Characteristics		
Age	60.2+6.8*CappedGaussian3	
Duration_Of_Diabetes	Max(0, CappedGaussian3*2+5)	
Male	Bernoulli(0.573)	
Race	Bernoulli(0.10)+1	1=White 2=Black
BMI	Max(0, Min(45, Gaussian(31.6,3.5)))	
Height	Iif(Male,1.7602+ 0.0742* CappedGaussian3, 1.6281+0.0699 * CappedGaussian3)	
SBP	149.8+21.4* CappedGaussian3	
DBP	83.4+11.3/21.4*Corr_SBP_DBP*(SBP-149.8)+CappedGaussian3*(1-Corr_SBP_DBP**2)*11.3	The function is mean_DBP+SD_DBP/SBP_SD*Corr_SBP_DBP*(SBP-mean_SBP)+CappedGaussian3*(1-Corr_SBP_DBP**2)*SD_DBP
Smoke	Bernoulli(0.278)	
HDLCholesterol	Max(0.3, Min(5, 1.19+0.33*CappedGaussian3))	
LDLCholesterol	Max(0.3, Min(11, 3.5+1.0*CappedGaussian3))	
Triglycerides	Max(0, Min(20,	

	Exp(Ln(1.7)+0.45*CappedGaussian3)))		
TotalCholesterol	HDLCholesterol+LDLCholesterol+Triglycerides*0.456		
HbA1c	Max(5.7, Min(30, Exp(CappedGaussian3*0.07+1.98)))		
AF	Bernoulli(0.05)		
Disease Status (Within each sub-model defined below, one and only one variable should be set to one)			
No_Cerebrovascular_Disease	Bernoulli(0.981)	Cerebrovascular disease sub-model	
Survive_Stroke	1-No_Cerebrovascular_Disease		
No_CVD	Bernoulli(0.939)	Coronary heart disease sub-model	
Angina[¥]	0		
CHFwoMI	0		
CADwProc	0		
Survive_MI	Iif(No_CVD+Angina, 0, 1)		
CHF[§]	0		
No_Nephropathy	Bernoulli(0.9)	Nephropathy sub-model	
Micro_Albuminuria	Iif(No_Nephropathy, 0, Bernoulli(0.30))		
Proteinuria	1- Micro_Albuminuria - No_Nephropathy		
ESRD_Dialysis	0		
ESRD_Transplant	0		
No_Neuropathy	Bernoulli(0.9)	Neuropathy sub-model	
Clinical_Neuropathy	1-No_Neuropathy		
Amputation	0		
No_Proliferative_Retinopathy_left	Bernoulli(0.78)	Left eye retinopathy sub-model	
Nonproliferative_left	Iif(No_Proliferative_Retinopathy_left, 0, Bernoulli(0.5))		
Proliferative_left	Iif(No_Proliferative_Retinopathy_left+Nonproliferative_left, 0, 1)		
Blind_Eye_left	0		
No_Proliferative_Retinopathy_right	Bernoulli(0.78)	Right eye retinopathy sub-model	
Nonproliferative_right	Iif(No_Proliferative_Retinopathy_right, 0, Bernoulli(0.5))		
Proliferative_right	Iif(No_Proliferative_Retinopathy_right+Nonproliferative_right, 0, 1)		
Blind_Eye_right	0		
No_Macular_edema_left	Bernoulli(0.90)	Left eye retinopathy sub-model	
Macular_edema_left	1-No_Macular_edema_left		
No_Macular_edema_right	Bernoulli(0.90)	Right eye retinopathy	

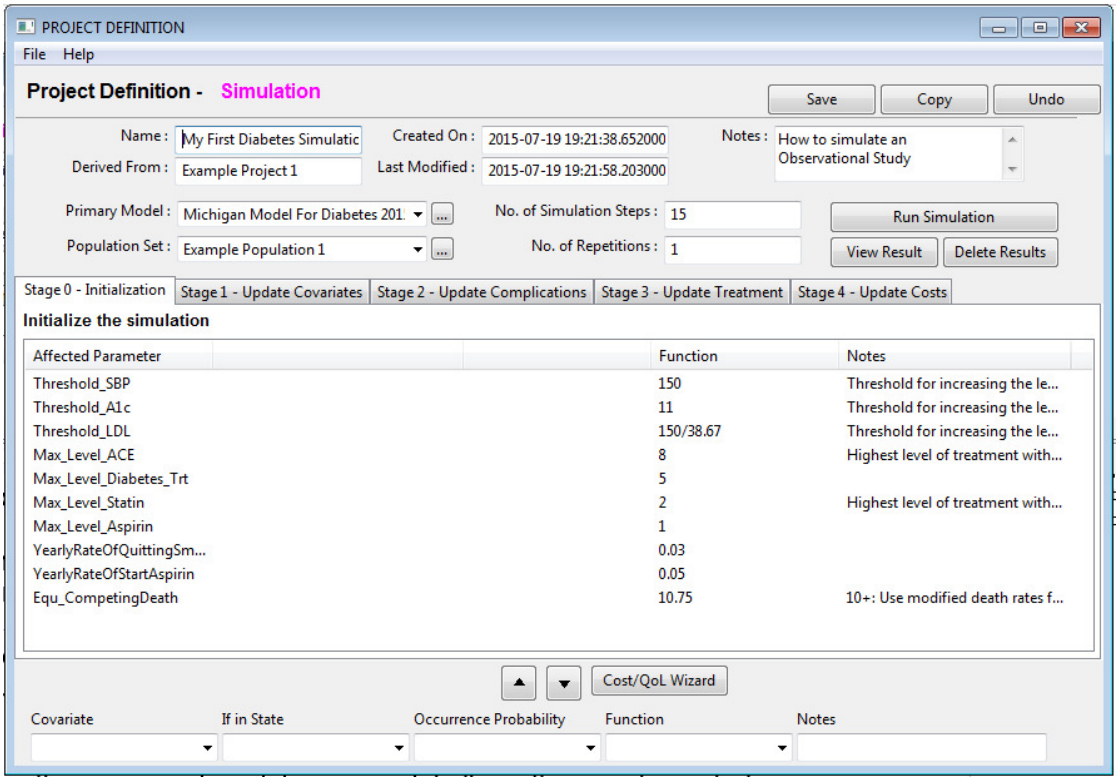
Macular_edema_right	1-No_Macular_edema_right	sub-model	
Medication			
IntensiveLifeStyle	Bernoulli(0.10)		
Metformin	Iif(IntensiveLifeStyle, 0, Bernoulli(3/9))		
OtherOralMedication	Iif(IntensiveLifeStyle+Metformin, 0, Bernoulli(2/6))		
BasalInsulin	Iif(IntensiveLifeStyle+Metformin+ OtherOralMedication, 0, Bernoulli(1/4))		
Insulin	Iif(IntensiveLifeStyle+Metformin+ OtherOralMedication+BasalInsul in, 0, 1)		
Beta_Blocker	Iif(Or(Survive_MI, Survive_Stroke), 1, Bernoulli((0.15-0.10)/(1-0.10)))		
Ace_Inhibitor	Iif(Or(Survive_MI,Survive_Stroke),1, Bernoulli((0.389 - 0.10)/(1-0.10)))		
Statin	Iif(Or(Survive_MI,Survive_Stroke),1, Bernoulli((0.531 - 0.10)/(1-0.10)))		
Aspirin	Iif(Or(Survive_MI,Survive_Stroke),1, Bernoulli((0.244 - 0.10)/(1-0.10)))		

[¥]This variable is an indicator for the state “CAD w/o MI” as in shown in Appendix A. For historical reason this variable name for this state was name as Angina in the software.

[§] This variable is an indicator for the state “CHF after MI” as in shown in Appendix A. For historical reason this variable name for this state was name as CHF in the software.

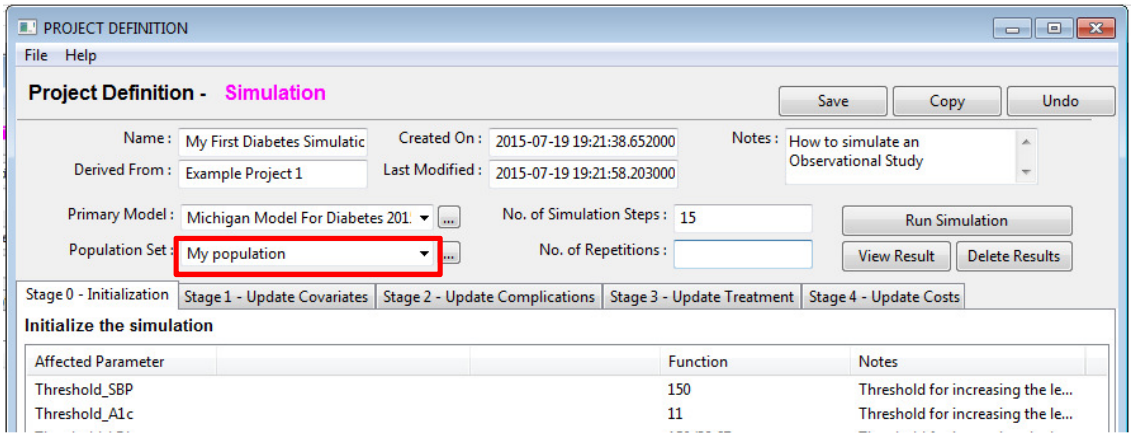
6 Running the Model

To run the model use the project window to set the following parameters and then to start the simulation.

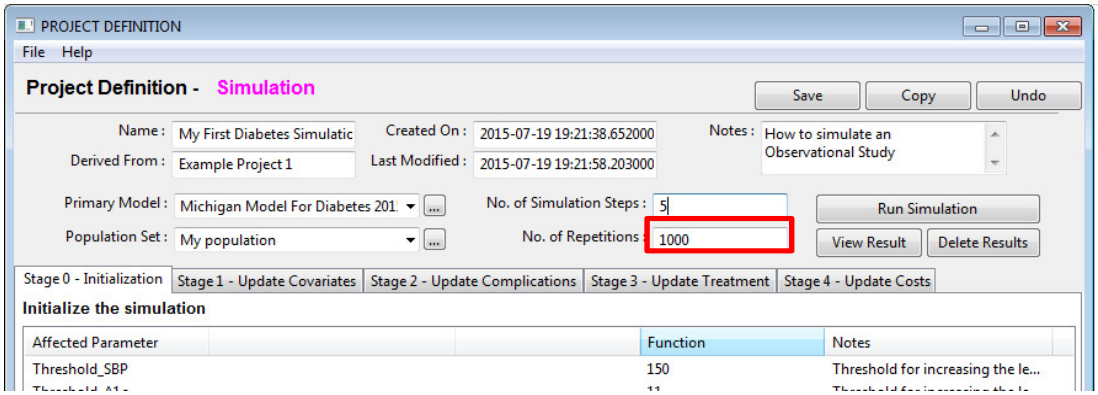


6.1. Select the population set and set number of subjects

Use the dropdown menu to select the **Population Set** you would like to conduct the simulation on.



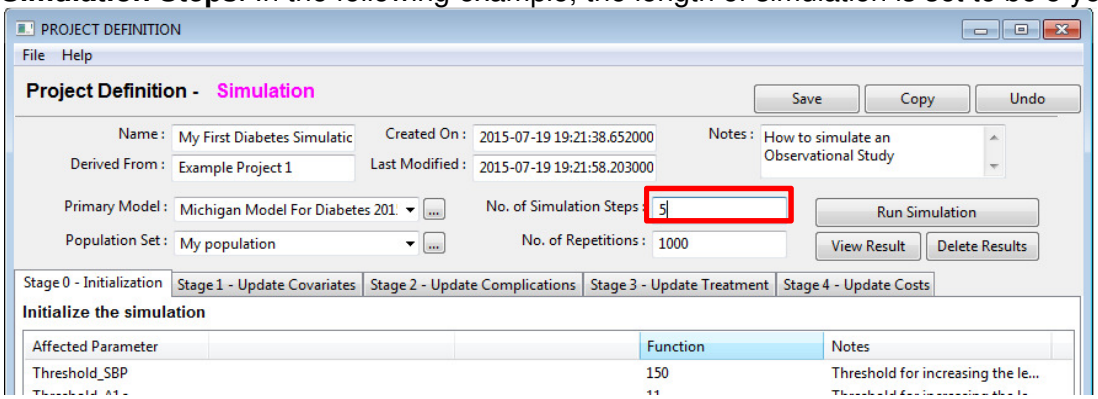
If you are using a population set defined by distributions, to set the number of subjects to be included in the simulation, write down the number of subjects in the small window of **No. of Repetitions**.



If you are using a population set with individual data, the number in the small window of **No. of Repetitions** tells the computer how many repetitions for each subject in your population set will be simulated. For example, if you have 100 subjects in the population set, and you set **No. of Repetitions** to be 2, the program will simulate 200 subjects in total.

6.2. Number of years simulated

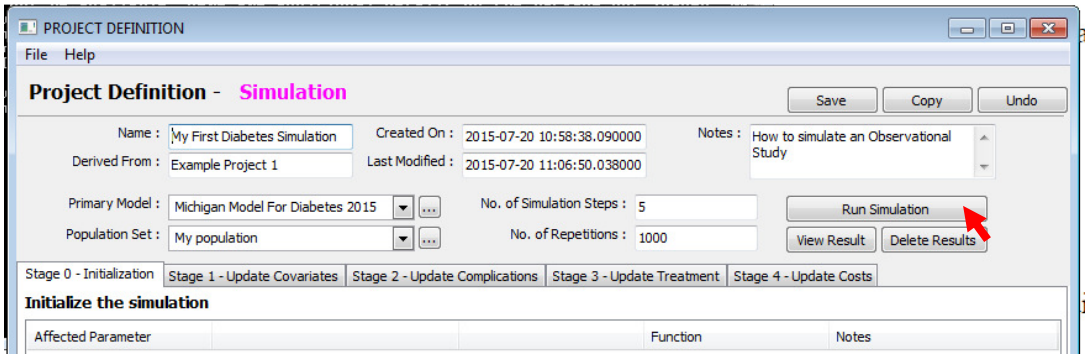
To set the length of the simulation, fill in the number of years to simulate in the small window of **No. of Simulation Steps**. In the following example, the length of simulation is set to be 5 years.



6.3. Run simulation

⚠ Save all the changes before running a simulation. Otherwise, if the program is aborted, all the changes will be lost.

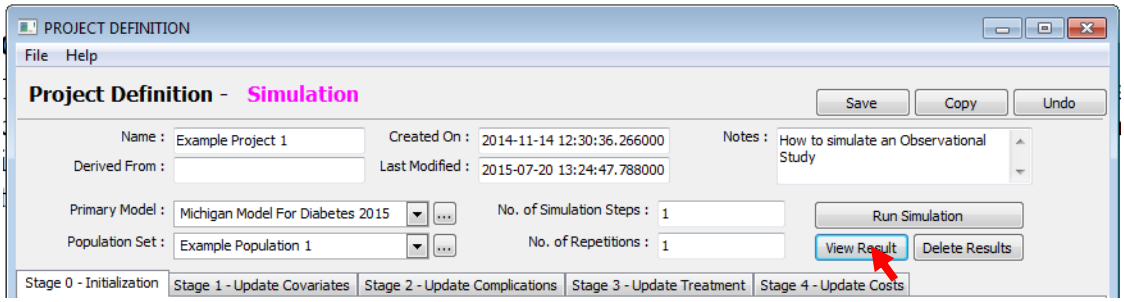
Click on the **Run Simulation** button to start the simulation.



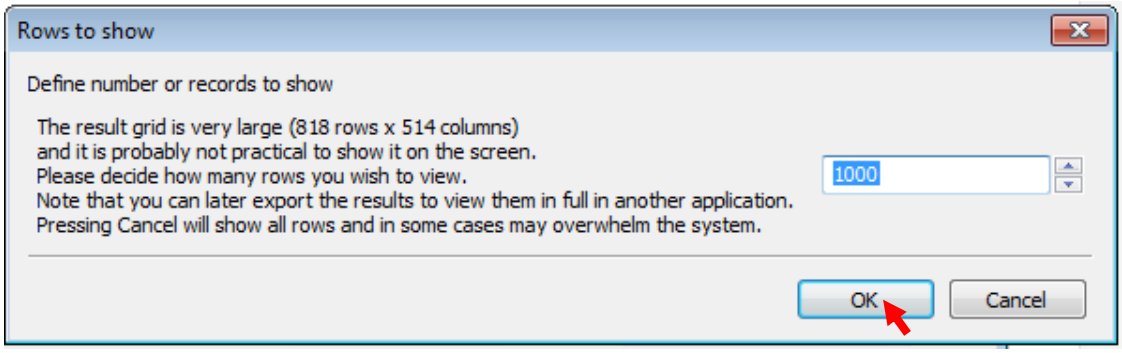
Once you start the simulation, a small window pops up to show how much time has elapsed since the simulation starts.

7 Outputs

When simulation is completed, click OK on the pop-up window that informs you the completion of the simulation. To view results, click on the **View Result** button.



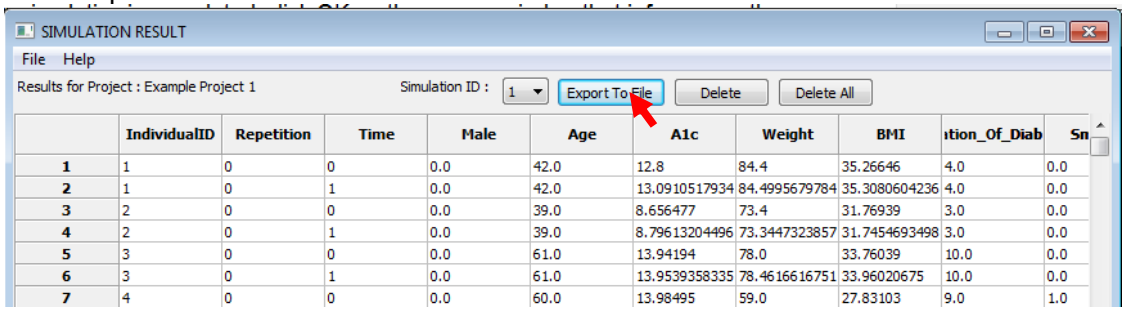
On the pop-up window, select the number of rows you would like to view in IEST and then click **OK**.



The following window shows the simulated yearly results for all the simulated individuals.

The current IEST software only provides limited results summaries. We suggest that users export the individual results to csv files and calculate summary statistics and perform additional analyses using other software. In the **Worked Example** section, we provide a few SAS programs for summarizing simulation results.

To export results, click on the **Export To File** button and follow the steps to select the desired path to save the results as a CSV file.



	IndividualID	Repetition	Time	Male	Age	A1c	Weight	BMI	ıtion_Of_Diab	Sn
1	1	0	0	0.0	42.0	12.8	84.4	35.26646	4.0	0.0
2	1	0	1	0.0	42.0	13.0910517934	84.4995679784	35.3080604236	4.0	0.0
3	2	0	0	0.0	39.0	8.656477	73.4	31.76939	3.0	0.0
4	2	0	1	0.0	39.0	8.79613204496	73.3447323857	31.7454693498	3.0	0.0
5	3	0	0	0.0	61.0	13.94194	78.0	33.76039	10.0	0.0
6	3	0	1	0.0	61.0	13.9539358335	78.4616616751	33.96020675	10.0	0.0
7	4	0	0	0.0	60.0	13.98495	59.0	27.83103	9.0	1.0

Once you have exported the results, it is a good practice to delete all the results using the **Delete All** button before you make further modifications to any parameters

under the project window (including steps in the Sections 4.1.2 – 4.1.4). Otherwise, no modifications on the project can be saved and would need to be re-done. This is a problem the future version of IEST will fix.

8 Worked Examples

Example #1

To determine the likely impact of a difference in HbA1c values at the time of diagnosed type 2 diabetes, say 11.0% *versus* 7.0%, on Life Expectancy and Quality Adjusted Life Expectancy for a fifty-year old white male patient, proceed as follows:

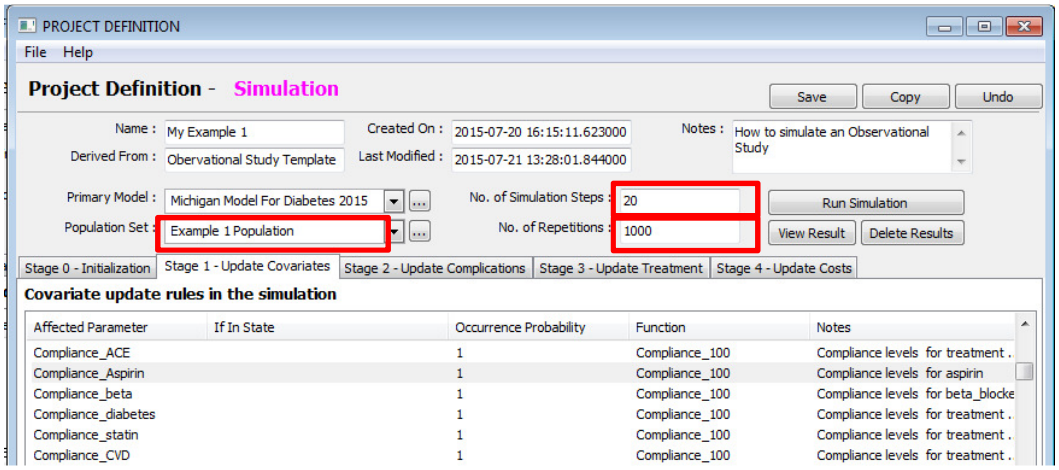
Step 1
Using the *Input Population Template.csv* file, enter characteristics for two patients that have identical risk-factor levels except for their HbA1c level.:

Variable Name	**Definition**	
System Variables		
Diabetes_Type_2	1	
Alive	1	
Demographics Characteristics		
Age	50 (years)	
Duration_Of_Diabetes	0 (year)	
Male	1 (Male)	
Race	1 (White)	
BMI	30 (kg/m^2)	
Height	1.80 (m)	
Current Risk Factors		
SBP	130 (mmHg)	
DBP	80 (mmHg)	
Smoke	0 (Non-smoker)	
HDLCholesterol	1.2 (mmol/L)	
LDLCholesterol	3.0 (mmol/L)	
Triglycerides	1.6 mmol/L	
TotalCholesterol	4.9 (mmol/L)	
HbA1c	7 (%) for subject one and 11 (%) for subject two	
AF	0	
Disease Status (Within the same sub-model defined below, one and only one variable should be set to one)		
No_Cerebrovascular_ Disease	1	No cerebrovascular disease
Survive_Stroke	0	
No_CVD	1	No coronary heart disease
Angina	0	
CHFwoMI	0	
CADwProc	0	
Survive_MI	0	
CHF	0	
No_Nephropathy	1	No nephropathy
Micro_Albuminuria	0	
Proteinuria	0	
ESRD_Dialysis	0	
ESRD_Transplant	0	
No_Neuropathy	1	No neuropathy

Clinical_Neuropathy	0	
Amputation	0	
No_Proliferative_Retinopathy_left	1	No left eye retinopathy
Nonproliferative_left	0	
Proliferative_left	0	
Blind_Eye_left	0	
No_Proliferative_Retinopathy_right	1	No right eye retinopathy
Nonproliferative_right	0	
Proliferative_right	0	
Blind_Eye_right	0	
No_Macular_edema_left	1	No left eye retinopathy
Macular_edema_left	0	
No_Macular_edema_right	1	No right eye retinopathy
Macular_edema_right	0	
Medication		
IntensiveLifeStyle	1	Currently use intensive life style for controlling glucose level
Metformin	0	
OtherOralMedication	0	
BasalInsulin	0	
Insulin	0	
Beta_Blocker	0 (Not taking beta-blocker)	
Ace_Inhibitor	0 (Not taking ACE inhibitor)	
Statin	0 (Not taking anti-dyslipidemia medication)	
Aspirin	0 (Not taking aspirin)	

Import this population sheet following instructions in section **5.1**.

Step 2
Follow instructions in section 4.1.1 to create a new observational project. On the project window, in the **Population Set** manual, select the population you have just created and read in. Set the **No. of Simulation Steps** to 20 (years), the **No. of Repetition** to 1000. To see how diabetes progresses in these two patients in the scenario that they both comply with all treatments, use the setup in the observational study template, change the compliance rate for all treatments to 100% (following instructions in Section 4.1.2). For all other parameters, use the default setting.

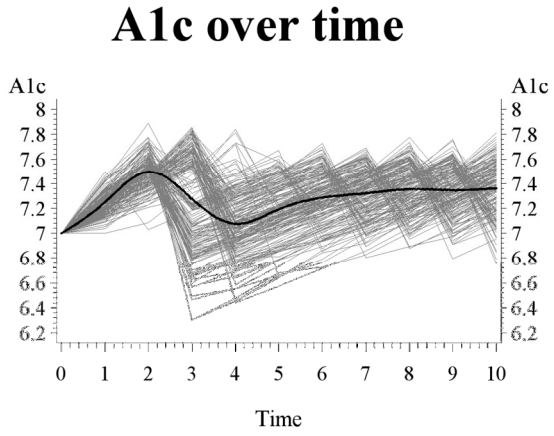


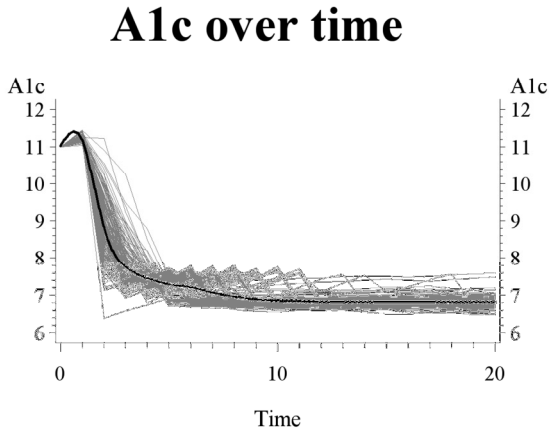
Step 3
Run the model and then export the data to a csv file. Use the included SAS program "Example1&2_Summary.sas" to summarize the simulation results. The default setting in this program summarizes the results for subject one. To get summaries on subject two, change the "if" statement in the first data step in the program.

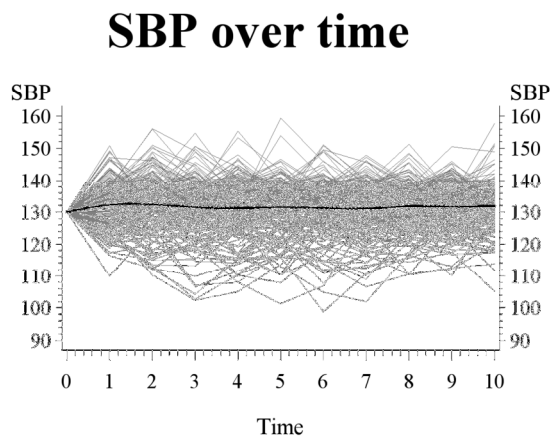
The quality-adjusted life expectancy for subject one should be approximately 18.6 ± 3.9 years (11.0 ± 2.3 QALYs) and for subject two, with the higher HbA1c at the beginning, slightly smaller at approximately years 18.5 ± 3.9 (10.6 ± 2.3 QALYs). Total cost is approximately $108,024 for subject one and $129,549 for subject two. Estimates may differ slightly between simulations as the MMD may have used a different set of random numbers.

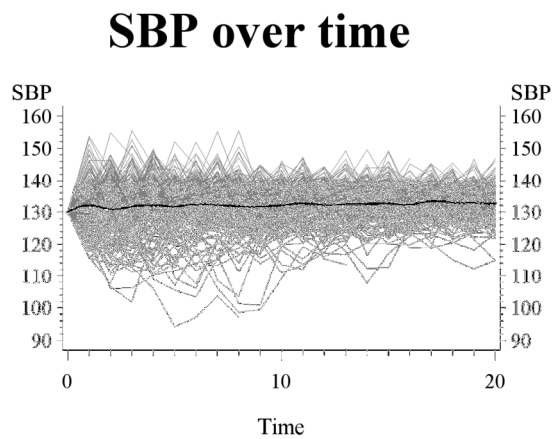
To generate these estimates, the model has simulated values for smoking status, total, LDL, & HDL cholesterol, systolic & diastolic blood pressure and HbA1c for each year, based on the baseline risk factor values entered, built-in treatment regimens, treatment threshold specified, and compliance rates. The following figures show the time paths for a few of these risk factors in subject one and subject two, respectively.

Subject One	Subject Two



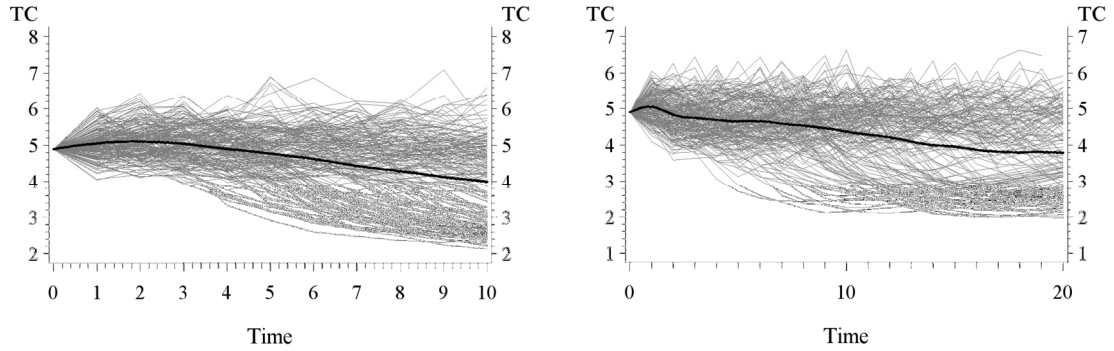






Subject One Subject Two

Total Cholesteroal over time Total Cholesteroal over time



It is also possible to examine cumulative event rates (adjusted for death as a competing risk) over the years specified in the simulation. The following table shows the simulated incidence rate for subject one and subject two per 1000 person-years (PYs). For example, for subject one, the estimated incidence rate of experiencing first MI is 5.7/1000 PYs; in 20 years, the probability for subject one to experience MI is 10.2%.

Complication	**Subject One**		**Subject Two**	
	Incidence rate (1000 PY)	**Cumulative Incidence (%)**	**Incidence rate (1000 PY)**	**Cumulative Incidence (%)**
MI	5.7	10.2	6.0	10.7
CHF	4.7	8.4	7.0	12.4
Stroke	1.5	2.8	2.0	3.7
Revascularization	8.2	14.5	8.4	14.6
Amputation	3.7	6.7	4.6	8.3
Blind In Both Eyes	0.38	0.7	0.37	0.7
ESRD	1.0	1.9	1.3	2.4
Cardiovascular Death	3.7	6.9	4.7	8.7
Death	9.3	17.4	10.1	18.7

Example #2

We may also want to undertake a simulation based on no compliance to any treatment at all. To study this, proceed as follows:

Step 1

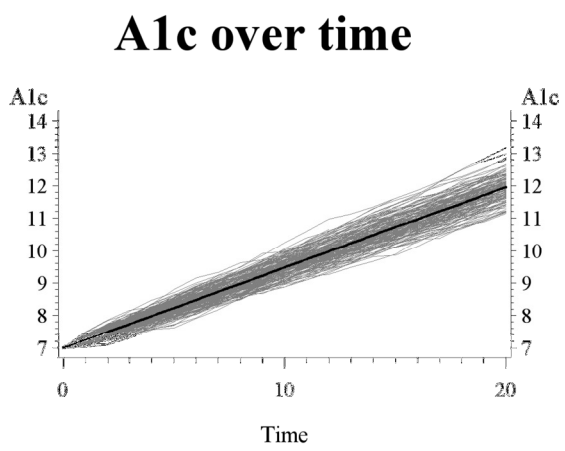
Use the project window in Example #1, change the compliance rate for all treatments to 0 (following instructions in Section 4.1.2).

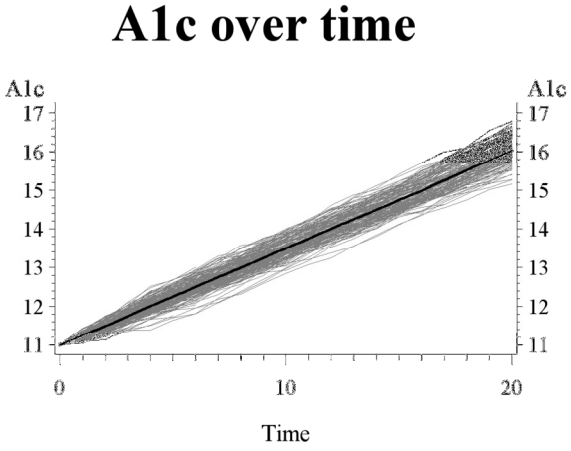
Step 2
Run the model and then export the data to a csv file. Use the SAS program "Example1&2_Summary.sas" to generate reports on the simulation results.

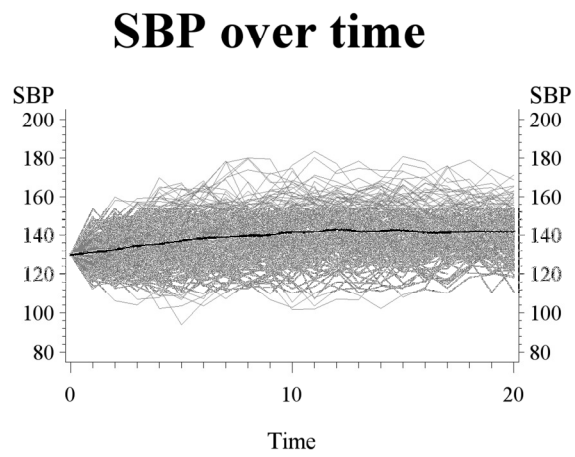
The quality-adjusted life expectancy for subject one should be approximately 17.6 ± 4.5 years (10.7 ± 2.8 QALYs) and for Subject two, with the higher HbA1c at the beginning, somewhat smaller at approximately 16.3 ± 5.0 years (9.9 ± 3.0 QALYs). Total cost is approximately $142,266 for Subject one and $170,612 for Subject two.

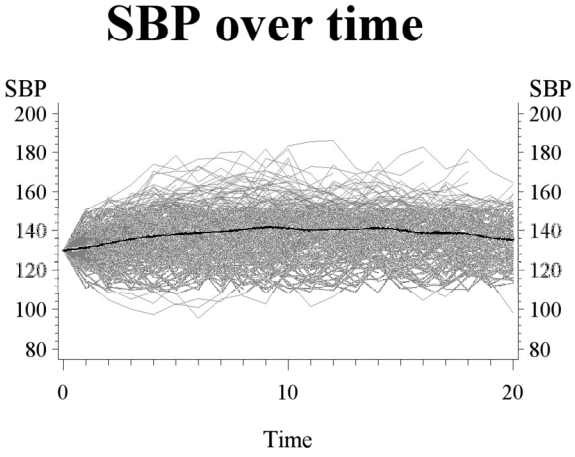
The following figures show the time paths for a few of these risk factors in Subject one and Subject two, respectively.

Subject One	Subject Two



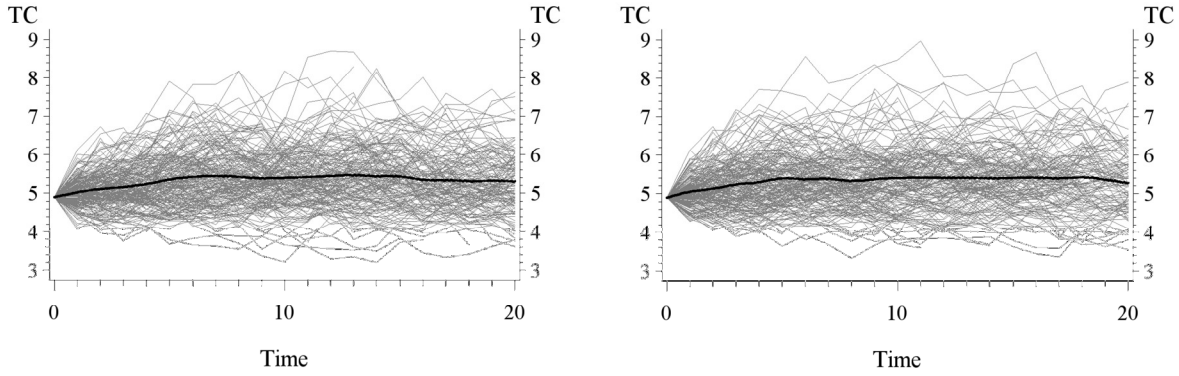






Subject One	Subject Two

Total Cholesteroal over time **Total Cholesteroal over time**



The following table shows the simulated incidence rate for subject one and subject one if neither of them complies with any treatment.

Complication	Subject One		Subject Two	
	Incidence rate (1000 PY)	Cumulative Incidence (%)	Incidence rate (1000 PY)	Cumulative Incidence (%)
MI	18.9	31.0	30.3	44.3
CHF	12.5	20.5	14.1	21.6
Stroke	3.7	6.4	6.4	10.4
Revascularization	28.1	43.0	41.4	54.4
Amputation	4.0	7.0	3.2	5.2
Blind In Both Eyes	0.23	0.4	0.24	0.4
ESRD	1.13	2.0	1.45	2.4
Cardiovascular Death	15.1	26.7	26.5	44.0
Death	19.3	34.3	31.9	52.8

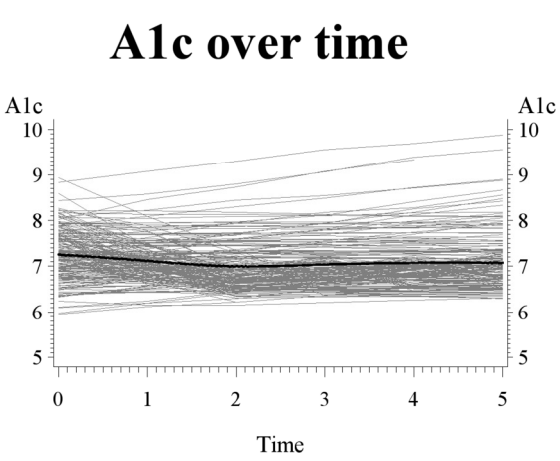
Example #3
Users may want to simulate disease progression for a population with known distributions of characteristics instead of a single subject. To undertake this type of simulation, proceed as follows:

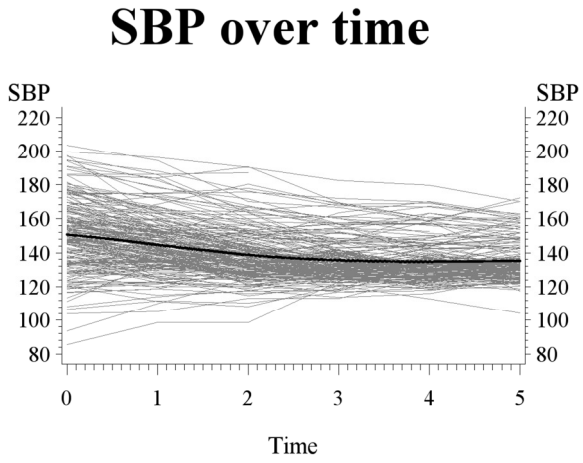
Step 1
Duplicate the project “Interventional Study Template” and rename it as Example 3. In the Population Set dropdown menu, select “Template for Specifying Distribution” (as shown in Section 5.2).

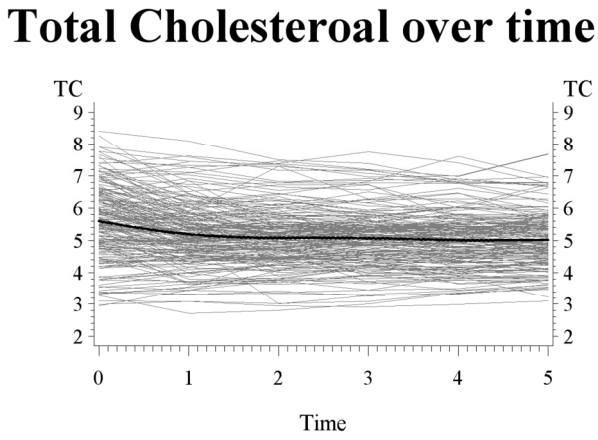
Step 2
Set the **No. of Simulation Steps** to 5 (years), the **No. of Repetition** to 5000. Use the default setting of interventional study template.

Step 3
Run the model and then export the data to a csv file. Use the included SAS program "Example3_Summary.sas" to generate report of simulation results.

The QALE should be approximately 2.80 ± 0.41 QALYs. Total cost is approximately $31,768. Estimates may differ slightly between simulations as the MMD may have used a different set of random numbers. To generate these estimates, the model has simulated values for smoking status, total, LDL, & HDL cholesterol, systolic & diastolic blood pressure and HbA1c for each year, based on the baseline risk factor values entered, built-in treatment regimens, treatment thresholds specified, and compliance rates. The following figures show the individual and population average time paths for a few of these risk factors.







The following table shows the simulated incidence rate for the simulate population in this example

Complication	Incidence rate (1000 PY)	Cumulative Incidence (%)
MI	7.6847	3.72
CHF	13.9845	6.66
Stroke	3.1596	1.54
Revascularization	11.2837	5.42
Amputation	0.5317	0.26
Blind In Both Eyes	0.1635	0.08
ESRD	1.7617	0.86
Cardiovascular Death	6.7824	3.32
Death	11.1134	5.44

Example #4

To obtain confidence intervals for life expectancy and quality-adjusted life expectancy estimates. (This feature is currently only available to internal users. The MMD group is working on providing it to external users).

9 Appendices

Appendix A: Michigan Model for Diabetes – Disease Progression Model

A1. Model Structure and Transition Probabilities

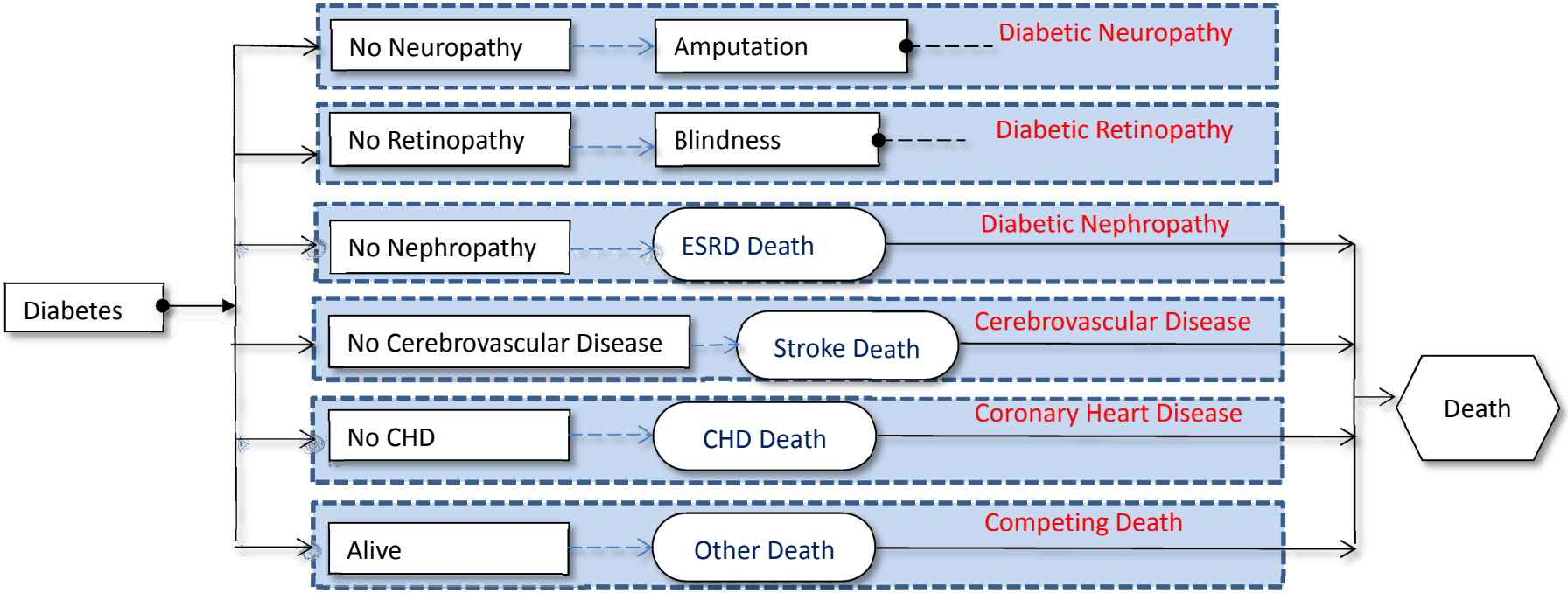


Figure A1. Overall Structure of Michigan Model for Diabetes.

Keys: Regular State; Event State; Module; Terminal State; Transition

Hidden transitions shown in Figures A2, A3, and A5 to A8

Splitting transition to multiple sub-processes

No transition initiated from the initial state, but the sub-process can be ended due to another sub-process reaches the terminal state

Nested parallel sub-processes

A1.1. Coronary heart disease (CHD) sub-model

A1.1.2. Structure and transition probabilities for CHD sub-model

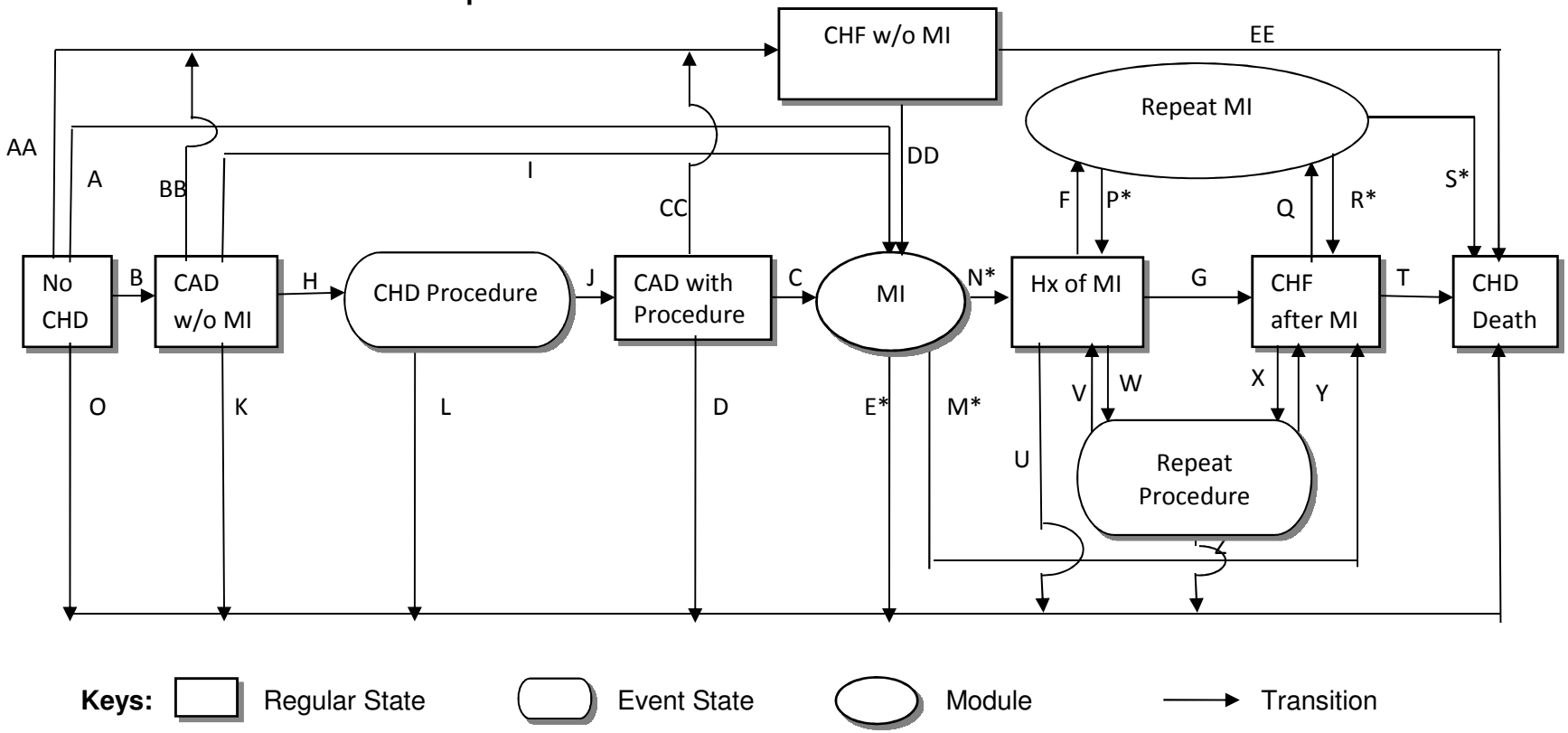


Figure A2. Coronary heart disease states and progression. CHD=coronary heart disease, CAD=coronary artery disease, CHF w/o MI=congestive heart failure without MI, MI=myocardial Infarction, CHF after MI=congestive heart failure after experience of MI, Hx=history, w/o=without, CHD procedure=revascularization procedure.

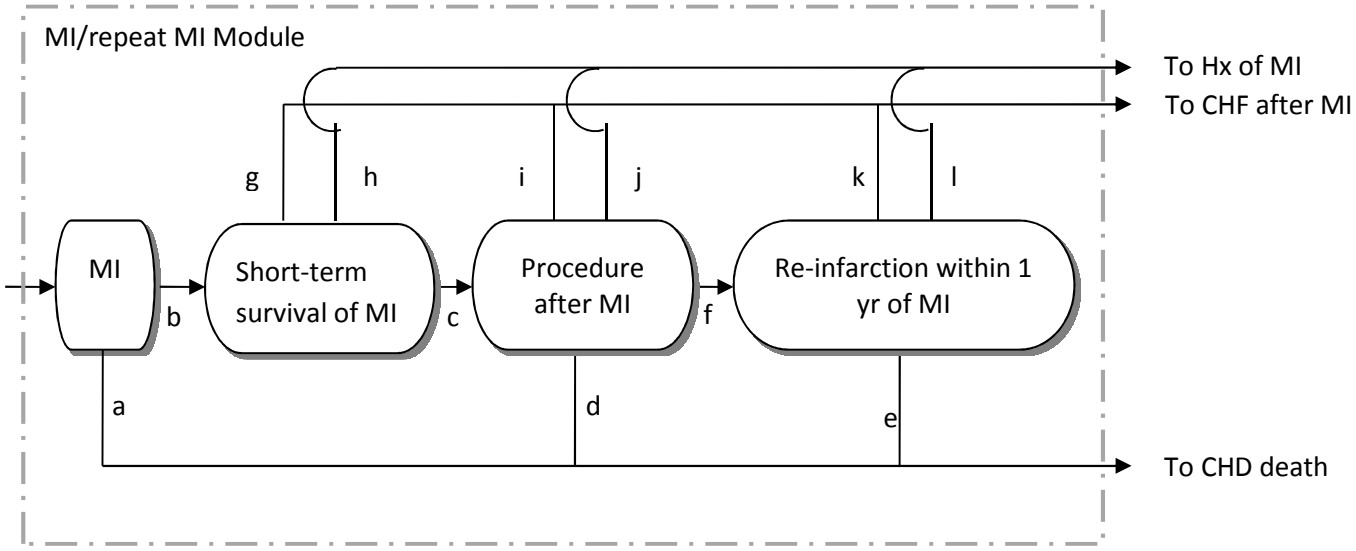


Figure A3. Myocardial infarction module. Ovals indicate instant states.

Table A1.Calibration and references for transition probabilities in the main CHD sub-model (Figure A2).

Transition	Transition Probability	Calibration	Risk factors	Reference
A (No CHD → MI	UKPDS MI equation (IHD=0, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.7.	Calibrated to Avogaro et al (2007) men and women separately	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Avogaro et al (2007)
B (No CHD → CAD w/o MI)	UKPDS IHD equation adjusted for medication benefit and by additionally adjusting the hazard function by a factor of 3.			
O (No CHD → CHD death)	UKPDS MI equation (IHD=0, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.091.			
AA (No CHD → CHF w/o MI)	CHS risk equation (Section C in this document; Angina=0, MI=0) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP et al. (1991)
K (CAD w/o MI → CHD death)	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.668.	Calibrated to Colhoun et al. (2004) placebo groups	Age, sex, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Colhoun et al. (2004)
I (CAD w/o MI → MI)	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 1.68.			
H (CAD w/o MI → CHD procedure)	The UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor 7.62.			
BB (CAD w/o MI → CHF w/o MI)	CHS risk equation (Section C in this document; Angina=1, MI=0) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
L (Immediate	5%	None	None	Cole (2002)

death after CHD procedure)				
J (Survive CHD procedure)	95%			
C (CAD with procedure → MI)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 1.387.	Calibrated to the prompt group in Chaitman et al. (2009)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Chaitman et al. (2009)
D (CAD with procedure → CHD death)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.37 based on calibration.			
CC (CAD with procedure → CHF w/o MI	CHS risk equation (Section C in this document; Angina=1, MI=0) adjusted for medication benefit		Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
DD (CHF w/o MI → MI)	UKPDS MI equation (IHD=1 if subjects had history of angina, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.07.	Calibrated to Deedwania (2011) and Mellbin et al (2011)	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Clarke et al.(2004); Deedwania (2011); Mellbin et al (2011)
EE (CHF w/o MI → CHD death)	UKPDS MI equation (IHD=1 if subjects had history of angina, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.43.	Calibrated to Deedwania (2011) and Mellbin et al (2011)	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Clarke et al.(2004); Deedwania (2011); Mellbin et al (2011)
E* (MI → CHD death)	See details in the MI/repeat MI module (Table A2)	See Table A2	See Table A2	See Table A2
M*(MI → CHF after MI)	See details in the MI/repeat MI module (Table A2)			

N* (MI → Hx of MI)	See details in the MI/repeat MI module (Table A2)			
U (Hx of MI → CHD death)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard function by a factor 0.232.	Calibrated to Jensen et al. (2011) and Mellbin et (2011)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Mellbin et al. (2011); Jensen et al. (2011)
F (Hx of MI → Repeat MI)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor by 1.247.			
W (Hx of MI→ Repeat procedure)	UKPDS MI equation (IHD=1, CHF=0) adjusted for medication benefit and by additionally adjusting the hazard by a factor by 3.074.			
G (Hx of MI → CHF after MI)	CHS risk equation (Section C in this document; Angina=1, MI=1) adjusted for medication benefit	None	Age at diabetes onset, sex, SBP, DBP, lipid ratio, BMI, history of angina, history of MI, AF, and medications[§].	Fried LP el al. (1991)
P* (Repeat MI → Hx of MI)	See details in the MI/repeat MI module (Table A2)	See Table A2	See Table A2	See Table A2
R* (Repeat MI → CHF after MI)	See details in the MI/repeat MI module (Table A2)			
S* (Repeat MI → CHD death)	See details in the MI/repeat MI module (Table A2)			
Q (CHF after MI→ Repeat MI)	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 1.088.	Calibrated to Deedwania (2011) and Mellbin et al (2011)	Age, gender, race, smoking, HbA1c, SBP, lipid ratio, and medications[§].	Clarke et al.(2004); Deedwania et al. (2011) Mellbin et al. (2011)
T (CHF after MI→ CHD death)	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 0.489.			
X (CHF after MI→ Repeat procedure)	The UKPDS MI equation (IHD=1, CHF=1) adjusted for medication benefit and by additionally adjusting the hazard by a factor 6.201			
V (Repeat procedure → Hx of MI)	95% if subject does not have CHF 0% if subject have CHF	None	None	Cole et al. (2002)

Y (Repeat procedure → CHF)	95% if subject have CHF 0% if subject does not have CHF	None	None	
Z (Repeat procedure → CHD death)	5%	None	None	

[§]Medications in this table refer to aspirin, lipid drug, ACE-inhibitor, and beta-blocker.

Table A2. Calibration and references for transition probabilities in MI/repeat MI module (Figure A3)

Transition	Transition Probability	Calibration	Reference
a (MI → CHD death: fatal MI)	MI: Modified the UKDPS fatality equation by add gender effect. The new odds of death is -3.251+2.772*Ln(Age/52.59)+(HbA1c-7.09)*0.114+2.640+Female*Ln(3.5) We then calculate the probability of death using the odds and adjusted by a factor 0.18, disregard whether a patient has CHF or not.	Calibrated to10% fatal MI for men and 15% fatal MI among all first MI events in Colhoun et al. (2004) study. These fatality rate is based on information in Roffi et al.(2013)	Clarke et al.(2004); Colhoun et al. (2004); Roffi et al. (2013)
	Repeat MI: For subjects with CHF: Using the probability from the modified odds as described above. For subjects without CHF: Using the probability from the modified odds further adjusted by a factor 0.53	Calibrated to Jensen et al. (2011)	Clarke et al.(2004); Jensen et al. (2011)
b (MI → Short-term survival of MI)	1-transition probability in a		Clarke et al.(2004); Colhoun et al. (2004); Roffi et al. (2013)
c (Short-term survival of MI → Procedure after MI)	MI: 75%	Jensen et al. (2011)	Franklin et al. (2004); Jensen et al. (2011) Deedwania (2011)
	Repeat MI: 63%	Jensen et al. (2011); Deedwania (2011)	
g (Short-term survival of MI → CHF after MI)	MI: 25%×P(CHF) †	Jensen et al. (2011)	
	Repeat MI: 37%×P(CHF) †	Jensen et al. (2011); Deedwania (2011)	
h (Short-term survival of MI → Hx of MI)	25%×(1-P(CHF)) †	Jensen et al. (2011)	
	Repeat MI: 37%×(1-P(CHF))†	Jensen et al. (2011); Deedwania (2011)	
d (Procedure after MI → CHD death)	MI: 12.5%	Jensen et al. (2011)	
	Repeat MI: 10%	Jensen et al. (2011); Deedwania (2011)	
f (Procedure after MI →Re-infarction within a year of MI)	MI: 8.75%	Jensen et al. (2011)	
	Repeat MI: 9%	Jensen et al. (2011); Deedwania (2011)	
i (Procedure after MI →	MI:	Jensen et al. (2011)	

CHF after MI)	For subject has CHF before MI: 78.75% For subject has no CHF before MI: 78.75%×P(CHF)†		
	Repeat MI: For subject has CHF before repeat MI:81%×P(CHF)† For subject has no CHF before repeat MI: 81%%×P(CHF)†	Jensen et al. (2011); Deedwania (2011)	
j (Procedure after MI → Hx of MI)	MI: For subject has CHF before MI: 0 For subject has no CHF before MI: 78.75%×(1-P(CHF))†	Jensen et al. (2011)	Franklin et al. (2004); Jensen et al. (2011)
	Repeat MI For subject has CHF before repeat MI: 0 For subject has no CHF before repeat MI: 78.75%×(1-P(CHF))†	Jensen et al. (2011); Deedwania (2011)	
e (Re-infarction within a year of MI → CHD death	17%	Jensen et al. (2011)	
k (Re-infarction within a year of MI → CHF after MI)	83%×P(CHF)		
l (Re-infarction within a year of MI → Hx of MI)	83%×(1-P(CHF))†		

†P(CHF)=0.13*Age_Modifier*Gender_Modifier*0.45*Medication_Modifier for MI module;
P(CHF)=0.13*Age_Modifier*Gender_Modifier Medication_Modifier for repeat MI module.

The age and gender modifier in the P(CHF) equations in Table A2 are shown in Table A3.

Table A3. Age and Gender Modifier in Table A2 (Franklin et al., 2004)

Factor	Category	Modifier
Age	<55	0.53
	55-64	0.87
	65-74	1.09
	>=75	1.51
Gender	Male	0.86
	Female	1.14

For example, for a 60 years old male subject not on beta-blocker or ACE-Inhibitor, P(CHF) for the MI module = 0.13*0.87*0.86*0.45
Medication_Modifier is as described in the main text.

A1.1.2 Prediction model for the risk of congestive heart failure (CHF) in type 2 diabetes (T2DM) based on the Cardiovascular Health Study

Data source

The Cardiovascular Health Study (CHS) was a study of risk factors for the development and progression of CHD and stroke in people aged 65 years of age and older. The 2,962 women and 2,239 men were recruited and examined yearly from 1989 through 1999. The added minority cohort of 256 men and 431 women was examined from 1992 to 1999. Examination components included medical history questionnaires, echocardiograms, ambulatory electrocardiograms, cerebral magnetic resonance imaging, abdominal and carotid ultrasound studies, measurement of ankle-brachial index, spirometry, and retinal photographs. CHS has undertaken extensive follow-up for ascertainment of cardiovascular events including myocardial infarction (MI), CHF, stroke, claudication, and death.

Our goal was to develop a long-term prediction model for CHF in T2D conditional on the subject's history of angina and MI. In the original CHS cohort, 862 subjects had diabetes at the baseline visit without history of CHF, including 416 who had newly diagnosed diabetes (incident cohort) and 446 had previously diagnosed diabetes (prevalent cohort). Duration of diabetes of the prevalent cohort is unknown. During the median follow-up 10 years, 308 subjects in the prevalent cohort and 134 subjects in the incident cohort developed CHF.

Predictors

Selection of potential predictors was informed by characteristics included in the UKPDS Outcome Models (I & II) (Clarke et al., 2004; Hayes et al., 2013) and Risk Equations for First and Second Cardiovascular Events from Swedish Register Data (Kiadaliri et al., 2013). Initially, 15 risk factors were selected as candidate predictors for the regression model, including history of angina, history of MI, history of angioplasty, history of bypass surgery, Atrial fibrillation (AF), most recent value of fasting glucose, LDL, lipid ratio (total cholesterol/HDL), SBP, DBP, BMI, sex, race, smoking status and age at CHS study baseline visit. Of these 15 risk factors, sex, race, smoking status, and age at baseline are time independent covariates. The other nine risk factors are time-dependent covariates.

Data analysis and model selection

Given that duration of diabetes is a very important risk factor for CHF (Kiadaliri et al., 2013), one would typically use the incident cohort only to derive the CHF prediction model. However, the smaller number of events in the incidence cohort limited the statistical power for model development. At least 10-20 events per candidate predictor have been proposed in previous guidelines for the development of prediction models (Harrell et al., 1984).

In order to overcome the problem caused by missing duration of diabetes in the prevalent cohort, and to make use of the information provided by this cohort, we employed the following analysis strategy. First, we used a Cox proportional hazard regression model stratified by cohort types (i.e. prevalent cohort and incident cohort). This model allowed us to derive a non-parametric estimation of baseline hazard function for each of the two cohorts separately, while using data from both cohorts to select predictors and estimate corresponding risk coefficients. By including data from both cohorts, we had a total of 442 CHF events which provided ~29 events per candidate predictor. This was more powerful than <10 events per candidate predictor

which the incident cohort alone would have provided. This model also allowed us to accommodate both time-independent and time-dependent predictors.

Second, in order to use the model for long-term prediction, we used a non-linear regression model to fit a Weibull cumulative hazard function to the estimated non-parametric cumulative baseline hazard function of the incident cohort derived from the Cox proportional hazard model.

The Weibull model assumes a baseline hazard given by the function:

$$h_0(t) = \rho t^{\rho-1} \exp(\lambda)$$

and the hazards model for the ith subject at time t is

$$h(t|x_i(t)) = h_0(t) \exp(\beta x_i(t)) = \rho t^{\rho-1} \exp(\lambda + \beta x_i(t))$$

where $x_i(t)$ is a vector of the risk factors for subject i at time t.

This two-step strategy allowed us to derive a Weibull proportional hazard model with time-dependent and time-independent predictors. Ideally, a one-step analysis to fit a Weibull proportional hazard model is preferred. However such a model requires modeling the multiple longitudinal factors simultaneously and no existing software is available. Figure S4 compares the non-parametric cumulative baseline hazard from the Cox proportional hazard model and the fitted Weibull function. The Weibull function fits the non-parametric function very well.

Before any modeling was performed, the distributions of all potential predictors were carefully examined for extreme values. Biologically implausible values were set to missing values, and the remaining extreme values were truncated by shifting the values below 1 centile and above 99 centile to “truncated points”. Such truncation may prevent distortion of the relationship between predictor and outcome due to high leverage of the extreme values.

To define appropriate transformation of continuous variables, we used p-spline functions to explore the potential nonlinear effect of potential continuous predictors. The only continuous predictor that has a non-linear function form is BMI. Based visual inspection, we assumed no BMI effect until centered BMI (centered at 28.2) $\cong$ 5, and a linear effect for centered BMI > 5. Therefore we used linear splines with one knot at BMI=33 (centered BMI=4.2) to model BMI effect. $\chi 2$ test showed that this transformed BMI variable provided a significantly better fit (p=0.012)

To select the best prediction model, we used a stepwise selection procedure with higher than standard p value. We used Akaike’s Information Criterium (AIC), which implies a p value <0.157 for selection of predictions with 1 df.

Results

The stepwise selection approach selected a model with 10 predictors. Estimated regression confidents are reported in Table A4. C-index for this model varies from 0.678 to 0.699 at 1 to 10 years, indicating acceptable discrimination. Using non-linear regression analysis we fitted a Weibull baseline cumulative function to the estimated non-parametric baseline function of the

incidence cohort strata (Figure A4). The estimated Weibull function parameters (ρ and λ) are also shown in Table A4.

Figure A4. Weibull baseline cumulative hazard functions.

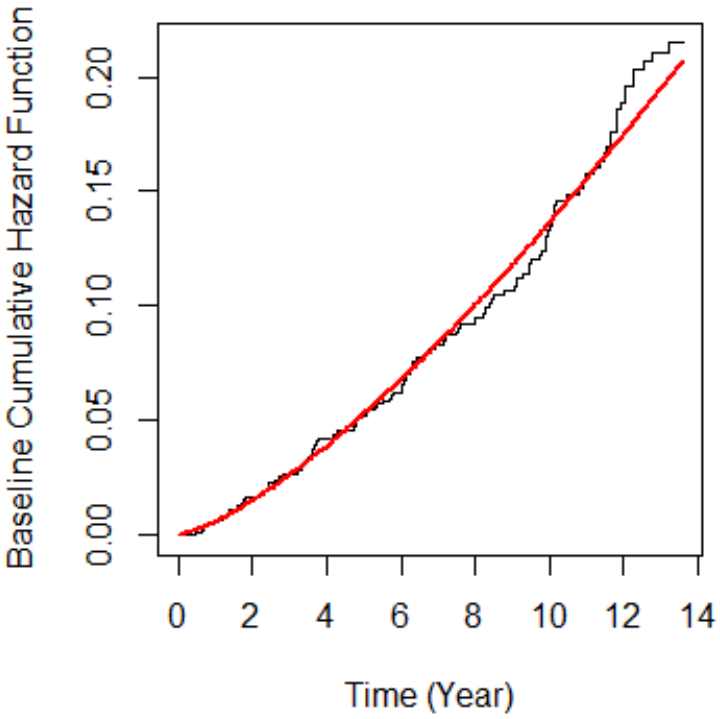


Table A4. Parameters in the prediction model for risk of congestive heart failure in T2DM

Parameter		Parameter Estimate	P-Value	Hazard Ratio (95% CI)
λ		-5.136		
ρ		1.364		
MI		0.665	<0.0001	1.95 (1.44, 2.62)
Angina		0.409	0.0039	1.51 (1.14, 1.99)
Ln TC/HDL (centered at 4.62)		0.782	0.00026	2.19 (1.44, 3.32)
SBP (centered at 136.9)		0.019	<0.0001	1.020 (1.013, 1.026)
DBP (centered at 69.4)		-0.017	0.0068	0.984 (0.972. 0.995)
BMI*	BMI (centered at 28.2)	0.004	0.81	1.00 (0.97, 1.04)
	BMI Plus function $(BMI-33)_+$	0.162	0.0057	1.18 (1.05, 1.32)
Gender: Male vs. Female		0.331	0.010	1.39 (1.08, 1.79)
AF: Yes vs. No		0.897	<0.0001	2.45 (1.56, 3.85)
Age at diabetes onset (centered at 65)		0.045	0.00037	1.05 (1.02, 1.07)
C index at 10 year		0.699		

*$(BMI-33)_+$ = BMI-33 when BMI-33>0, otherwise 0.

A1.2. Cerebrovascular disease sub-model

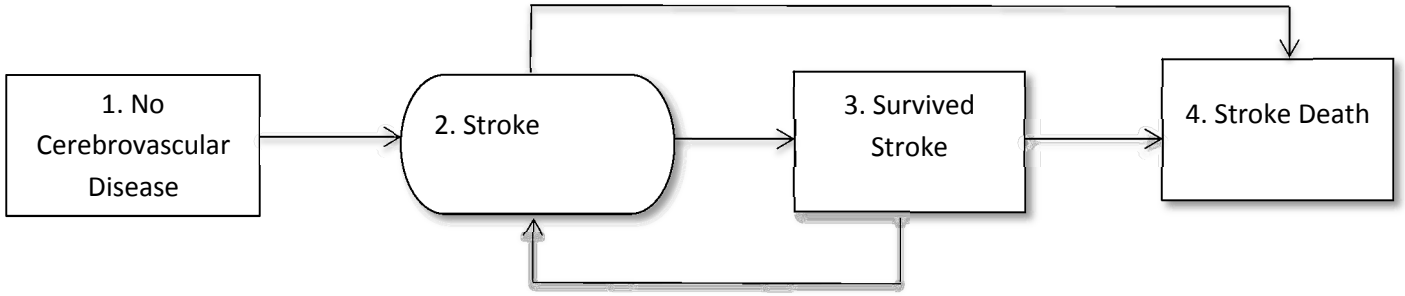


Figure A5. Structure of cerebrovascular disease sub-model

Table A5. Transition probabilities in cerebrovascular disease sub-model

Transition	Transition probability	Comments
1 to 2	Stroke hazard function from UKPDS 68 (Clarke et al., 2004) outcomes model modified by direct medication effect	
2 to 3	Complementary to Stroke to Stroke Death	This is the complementary for the transition from Stroke to Stroke Death. Changes in that transition should be reflected in this probability.
2 to 4	Fatality equation from UKPDS 68 (Clarke et al., 2004)	
3 to 2	If had stroke last year: 30 × transition probability of 1 to 2 If had stroke before last year: 10 × transition probability of 1 to 2	The calibration factor was influenced by numbers in table 2 in Sacco et al. (1994)
3 to 4	0.5*0.1064	Table 2 in Sacco et al. (1994): Similar to the existing diabetes formula that distinguishes the first year from subsequent years combine the following numbers (in %): first year = 0.201 and other years = 0.0738 ~ 1-((1-0.412)/(1-0.201))**(1.0/4)=0.0738. The above probability was multiplied by a calibration factor of 0.5 to reflect the advance in healthcare since 1994 in this scope. The multiplier is somewhat an arbitrary assumption and should be improved in the future with concrete evidence.

A1.3. Nephropathy sub-model

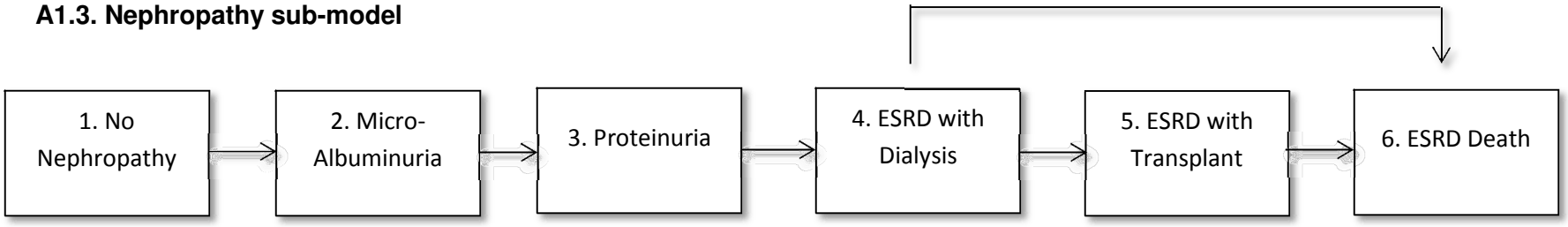


Figure A6. Structure of nephropathy sub-model

Table A6. Transition probability in nephropathy sub-model

Transition	Transition probability	Comments
1 to 2	0.0509	Gall et al. (1997) - number for 5 year progression in key messages p.787 is 0.23. Adjusted for 1 year from 5 years. ~ 1-(1-0.23)**(1/5)
2 to 3	0.1032	Ravid et al. (1993) (the risk for developing this degree of proteinuria within 5 years of follow-up was 19/45 (42%) in the placebo group. Number adjusted for 1 year from 5 years: 0.1032 ~ 1-(1-0.42)**(1/5)
3 to 4	0.0082	Humphrey et al. (1989): page 791, page 791, after 5 year, 7.0%, 8.4% developed it by 10 years and 11.6% by 15 years, the 15 year number was selected. Number adjusted for 1 year from 15 years: 0.0082 ~ 1-(1-0.116)**(1/15)
4 to 5	0.006 to 0.084 depends on age, gender, and race,	This data of the renal transplant rates in dialysis patients in year 2013 was provided by KECC at the University of Michigan. The data was processed using the following criteria: 1) only the data for diabetes as ESRD cause was selected; 2) the data depended on age, gender, and race; 3) the data for White and Black was selected; 4) the data was divided by 100 to represent the yearly transition probability; and 5) the case counts for 0-21 age groups were probably too low to report the rates appropriately, and thus the transplant rates in 22-44 age groups were used for 0-21 age groups.
4 to 6	0.0434 to 0.5472 depends on gender, age, race, Hypertension (adjusted by other death causes)	Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2015;66(1) (suppl 1):S1-S306. Table H.4.1 in Section H. Available at: http://www.usrds.org/reference.aspx (cited: 08/25/2015) The data from the USRDS

		table was processed using the following criteria: 1) only the data for diabetes was selected; 2) the data depended on age, gender, and race; 3) the data for non-Hispanic White and Black in the race columns was selected; and 4) the data was divided by 1,000 to represent the yearly transition probability.
5 to 6	0.0081 to 0.245 depends on gender, age, race, Hypertension (adjusted by other death causes)	Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2015;66(1)(suppl 1):S1-S306. Table H.10.1 in Section H. Available at: http://www.usrds.org/reference.aspx (cited: 08/25/2015) The data from the USRDS table was processed using the following criteria: 1) only the data for diabetes was selected; 2) the data depended on age, gender, and race; 3) the data for non-Hispanic White and Black in the race columns was selected; and 4) the data was divided by 1,000 to represent the yearly transition probability.

A1.4. Neuropathy sub-model

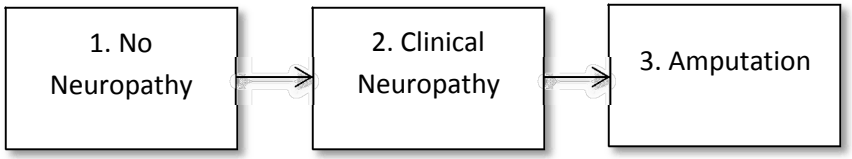


Figure A7. Structure of neuropathy sub-model

Table A7. Transition probabilities in neuropathy sub-model

Transition	Transition probability	Comments
1 to 2	0.0518	Sands et al. (1997), Table 1 - first line. Note that in the future it may be possible to use sex or age covariates using the same table data.
2 to 3	0.0113	Adler et al. (1999), Table 4 - last row. Note that the table considers only men, in the future other data may be considered.

A1.5. Retinopathy sub-model

Two eyes are modeled separately and assume to be independent. Retinopathy, macular edema are two parallel sub-sub-processes.

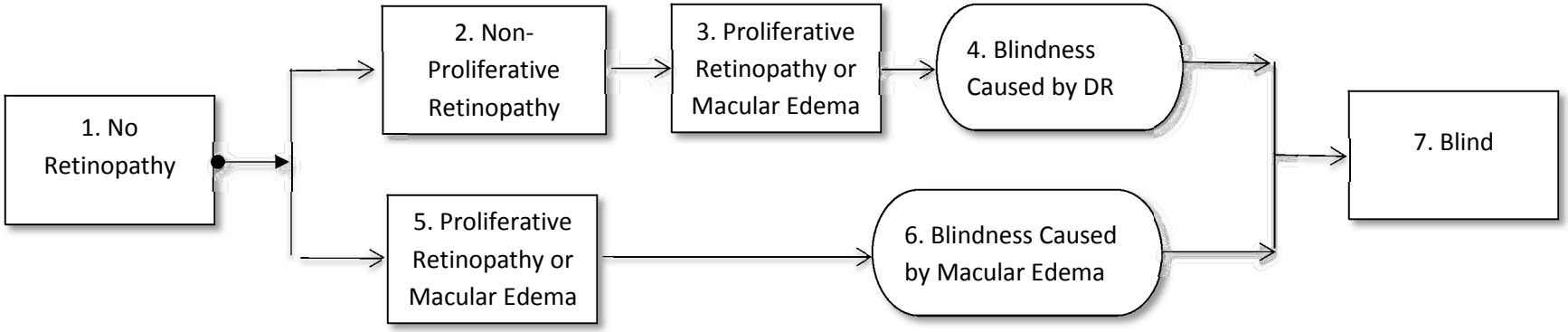


Figure A8. Structure of retinopathy sub-model

Table A8. Transition probabilities in retinopathy sub-model

Transition	Transition probability	Comments
1 to 2	0.0653 for diabetics who do not need Insulin treatment	Klein (1994), Table 8: 70.2% 10-yr progression rate was used for insulin-taking group and 49.1% 10-yr progression rate was used for non-insulin-taking group. The first row and the progression column for both categories were selected. Numbers were adjusted for 1 year progression 0.1140 ~ 0.114024676 = 1- (1-0.702)**(1/10), 0.0653 ~ 0.065301 = 1- (1-0.491)**(1/10).
	0.1140 for diabetics who need Insulin treatment	

2 to 3	0.0390 for diabetics need Insulin treatment 0.0233 for diabetics who do not need Insulin treatment	Klein et al. (994), Table 8: 70.2% 10-yr progression rate was used for insulin-taking group and 49.1% 10-yr progression rate was used for non-insulin-taking group. The first row and the progression column for both categories were selected. Numbers were adjusted for 1 year progression 0.1140 ~ 0.114024676 = 1- (1-0.702)**(1/10), 0.0653 ~ 0.065301 = 1- (1-0.491)**(1/10). For IGT, the probability is from Ref F1 Table 3. The nondiabetic retinopathy incidence after 5.6 years is 24 out of (24+278). When this is converted to yearly probabilities, we get: 1-(1-24.0/(24+278))**(1/5.6) = 0.014677981118243144 ~ 0.0147. Retinopathy is assumed to be non-proliferative for IGT since our model does not allow non diabetic proliferative retinopathy.
3 to 4	0.0148 for diabetics need Insulin treatment 0.0166 for diabetics who do not need Insulin treatment	Moss et al. (1994), Table 2: Only older onset numbers were used, the last 4 rows were used (Severity 60-85 - PDR) Incidences were calculated from multiplying % Incidence with Number of risk at each row. Both rounded and not rounded incident counts were close. The rounded calculation was selected. The sum of incidences was divided by the total number at risk to obtain the 10 year probability. The 1 year equivalent transition probabilities were calculated. Since there were no incidences of Blindness for non-taking Insulin at this age group, an assumption is made. The assumption is that the chance of blindness from Proliferative is the same as the probability from Non-Proliferative. These numbers are temporary and require modification
1 to 5	0.0308	Klein et al. (1995), Table 3: Numbers were calculated by summing all the incidents from all rows in the table except the first and last rows. Only older onset numbers were used. Incidences were calculated from multiplying % Incidence with Number of risk at each row. Both rounded and not rounded incident counts were close. The rounded calculation was selected. The sum of incidences was divided by the total number at risk to obtain the 10 year probability. The 1 year equivalent transition probabilities were calculated. See the XL spreadsheet for detailed calculations.
5 to 6	0.0148 for diabetics need Insulin treatment 0.0166 for diabetics who do not need Insulin treatment	It was decided to use progression probabilities similar to the transition from Proliferative to blindness. The reason these were used is that Moss et al. (1994) Table 3 shows Macular Edema has similar loss in the visual angle to Proliferative retinopathy in the taking insulin column (60.7 vs. 52.0, 69.2, 50.0, 81.2). This is an assumption that will be kept until a reference with more information is introduced. Note that for non insulin takers, the number actually originates from the non-proliferative to Blindness transition since the proliferative to Blindness transition inherits this number.
4 to 7	1	
6 to 7	1	

A1.6. Other death

Table A9. Transition probabilities for death due to non-diabetic causes

Process Competing Death	Transition probability	Comments
Alive to Other Death	0.0006 to 0.0546 depends on age, gender, race (adjusted by other death causes)	The data was retrieved from http://www.cdc.gov/nchs/hdi.htm, in which the table topic of "Mortality and life expectancy" was selected and then the table of "Mortality by underlying and multiple cause, ages 18+: US, 1981-2013 (Source: NVSS)" was selected. "Rates (underl.)" was selected in the "Measure" section, and the data of year 2013 was used. The rates of death due to "non-diabetic causes" were calculated as a summary of all death rates with a given cause selected as the underlying cause of death, except for diabetes, major cardiovascular diseases, and kidney diseases. Thus, these data would represent deaths from causes other than those that have been already counted in other sub-models, and these data depended on age, gender, and race/ethnicity.

A2. Cardiovascular risk factors and related treatments

Besides glycemia level, we also model weight/BMI, lipid profiles and systolic and diastolic blood pressures (SBP and DBP). Each year, the model updates glycaemia level and other cardiovascular risk factors before calculating transition probabilities for each of the six sub-models. In order to correctly model the casual relationships between these risk factors, we update them in the following order:

1) Weight
2) HbA1c
3) Lipids
4) SBP and DBP

The changes in these risk factors are determined by both treatment statues and aging/disease progression. When a patient is on lifestyle intervention only, changes in BMI drives the changes in HbA1c. When a patient is on oral/non-insulin glucose control drug(s) or insulin, the drug affects the changes in HbA1c and weight independently (which might not be the case; but we do not have data),

including the changes in the first year when the new treatment is initiated and the following years before next step of intensification of the treatment.

This set of models also models a causal relationship between different types of biomarkers. For example, the prediction models for lipids changes include both BMI and HbA1c changes as predictors, thus allow changes in BMI and HbA1c drive the changes in lipids. The other example is that changes in BMI drive the changes in DBP and SBP.

A2.1. Changes in Weight and BMI

BMI changes is derived from weight changes

Table A10. Changes of body weight under different anti-hyperglycemia treatment

Anti-hyperglycemia treatment	Initial effect (first year change)	Changes after one year	Comments
No treatment	N/A	Mean change=0.8kg/year SD of change=0.3kg/year	
Intensive lifestyle (diet and exercise/weight loss)	Mean change=-3.7kg SD of change=3.5kg	Mean change=1 kg/year SD of change=0.3kg/year	Baseline 80.4kg (SD 15.6 kg) UKPDS 13 (1995)
Metformin (one OAD/non-insulin med)	Mean change=-2kg SD of change=0.3kg	Mean change=-0.3kg/year SD of change=0.3kg/year	Kahn et al. (2006)
Metformin + Sulfonylureas (two OADs/non-insulin meds)	Mean change=2kg SD of change=1kg	Mean change=0 kg/year SD of change=0.3 kg/year	Phung et al. (2010)
Add Basal insulin to OAD/non-insulin med	Mean change=1.9kg SD of change=4.2kg	Mean change=0.8kg/year SD of change = 0.5kg	Holman et al. (2009)
Intensive insulin therapy	Mean change=1.2kg SD of change=0.5kg	Mean change=0.8kg/year SD of change=0.5kg/year	Rosenstock et al. (2009)

A2.2. Changes in HbA1c

There are 6 levels in glycemic control treatment:

0: No treatment
1: Diet and exercise
2: Oral/non-insulin medication (metformin)
3: Two oral/non-insulin medications (metformin + sulfonylureas)
4: Basal insulin
5: Intensive bolus insulin

Changes of HbA1c for patients under each treatment is described in Table A11. Patient will transition to next stage when HbA1c level becomes ≥ 7%

Table A11. Changes of HbA1c under different anti-hyperglycemia treatment scenarios

Anti-hyperglycemia treatment	**Initial effect (first year change)**	**Changes after one year**	**Comments**
Treatment Level 0: No treatment	N/A	Mean change=0.35%/year SD of change=abs(mean change)/3	This way HbA1c will increase about 2% in 6 years on average for diabetics who are not appropriately treated. UKPDS Group (1998) Figure 2 showed 1.5% increase in 6 years. It was arbitrarily increased to reflect faster increase without any treatment. An arbitrary variation was added to allow the change to be between zero and twice the value calculated from the references.
Treatment Level 1: Intensive lifestyle (diet and exercise/weight loss)	Mean change=-1.9%-0.5*(currentHbA1c-9.1%) SD of change=abs(mean change)/3	Mean change=0.2%/year SD of change=abs(mean change)/3	UKPDS 13 (1995)* UKPDS 33 (1998)#
Treatment Level 2: Metformin (one OAD/non-insulin med)	Mean change=-1.0%-0.5*(currentHbA1c-8.3%) SD of change=abs(mean change)/3	Mean change=0.14%/year SD of change=abs(mean change)/3	Sherifali et al. (2010)* Kahn et al. (2006)#
Treatment Level 3: Metformin + Sulfonylureas (two	Mean change=-0.8%-0.5*(currentHbA1c-8.3%) SD of change=abs(mean change)/3	Mean change=0.2%/year SD of change=abs(mean change)/3	Phung et al. (2010)* Charbonnel et al. (2005)#

OADs/non-insulin meds)			
Treatment Level 4: Add Basal insulin to OAD/non-insulin med	Mean change=-0.8%-0.5*(currentHbA1c-8.4%) SD of change=abs(mean change)/3	Mean change=0.2%/year SD of change=abs(mean change)/3	Holman et al. (2007)* Rhoads et al. (2011)#
Treatment Level 5: Intensive insulin therapy	Mean change=-1.2-(CurrentHbA1c-8.2)*0.5 SD of change=0.326	No change	Holman et al. (2009)* Since the individuals in the 4T-study did receive intensive insulin therapy after one year of basal insulin, most of them had already an HbA1c < 8.0%. Baseline HbA1c before initiation of intensive therapy was 7.6% and median HbA1c after 2 years was 6.9% (CI 6.6 to 7.1%). Therefore, we would change the decrease in HbA1c using intensive insulin for our model to 1.0% (SD 0.1).

*Reference for initial change
#Reference for change after one year

A2.3. Changes in lipids

Every year, the change of lipid is calculated by adding initial change induced by treatment change, if any, and the change following that, which can be attributed to aging or disease progression.

Drug effect: Currently, we model two levels of treatment for dyslipidemia. For each of these two levels, the drug-induced change is 25% decrease, 5% increase, and 6% increase in LDL-C, HDL-C, and triglyceride, respectively.

Aging effect:
x1, x2, x3 are three randomly drawn independently distributed standard normal variables. They are redrawn each year.
The three following equations calculate the change in logarithm (e-based) transformation of HDL, LDL, and triglyceride based on the current value of Ln_HDL, Ln_LDL, Ln_triglyceride, change in BMI, change in logarithm (e-based) transformed fasting glucose, and gender

Diff_Ln_HDL Change=0.0340+Age*(-.00112)+Age*Age*0.0000117+Ln_Triglycerides*(-.0145)+Ln_LDL*(-.000961)+Ln_HDL*(-.0844)+Diff_Ln_FastingGlucose*(-.0364)+Diff_BMI*(-.00414)+Female*(0.0147)+0.0648*x3

Diff_Ln_LDL=0.0738+Age*0.00412+Age*Age*(-.0000463)+Ln_Triglycerides*(0.0114)+Ln_LDL*(-.138)+Ln_HDL*(0.00620)+Diff_Ln_FastingGlucose*0.0821+Diff_BMI*0.00906+Female*0.00600+0.111*x2+0.00206*x3

Diff_Ln_Triglyceride=-.157+Age*0.00728+Age*Age*(-.0000660)+Triglycerides_Ln*(-.112)+Ln_LDL*0.0189+Ln_HDL*(-.0496)+Diff_Ln_FastingGlucose*0.268+Diff_BMI*0.0275+Female*0.0215+0.1359*x1+0.00734*x2-0.0189*x3

Diff_Ln_HDL: future change in Ln_HDL
Diff_Ln_LDL: future change in Ln_LDL
Diff_Ln_triglyceride: future change in Ln_triglyceride
Ln_HDL: logarithm (e-based) transformed current HDL
Ln_LDL: logarithm (e-based) transformed current LDL
Ln_Triglycerides: logarithm (e-based) transformed current triglyceride
Diff_Ln_FastingGlucose: future change in logarithm (e-based) transformed current fasting glucose (mmol/L)
Diff_BMI: future change in BMI

A2.4. Changes in blood pressure

Drug effect:

We assume a patient can go through a maximum of 9 levels of anti-hypertensive treatments, including no treatment:

0: No anti-hypertensive treatment
1: one drug half dose
2: one drug full dose
3: two drugs half dose
4: two drugs full dose
5: three drugs half dose
6: three drugs full dose
7: four drugs half dose
8: four drugs full dose

ACE-inhibitor/ARB will be the first drug to be added regardless of whether a patient is receiving β-blocker or not.

Table A12. Effect of anti-hypertensive treatment

Anti-hypertensive treatment change	**Drug effect**	**Comments**
No treatment		
No drug → one drug half standard dose	If the first drug is ACE-inhibitor/ARB: Mean change of SBP=-6.9mhg-0.08(SBP-150) Mean change of DBP=-3.7mhg-0.09(DBP-90) If the first drug is β-blocker: Mean change of SBP=-7.4mhg -0.08(SBP-150) Mean change of DBP=-5.6mhg-0.09(DBP-90)	Law et al. (2009); Wald et al. (2009); Law et al. (2003)
Already on drug → receive an increase of treatment of n levels	Mean change of SBP=-n×3.4mhg- n×0.04(SBP-150) Mean change of DBP=- n×1.8mhg- n×0.04(DBP-90)	
No drug → treatment level n (n>1)	If the first drug is ACE-inhibitor/ARB: Mean change of SBP=-6.9-n×3.4mhg-(0.08+n×0.04)×(SBP-150) Mean change of DBP=-3.7-n×1.8mhg-(0.09+n×0.04)×((DBP-90) If the first drug is β-blocker: Mean change of SBP=-7.4mhg -n×3.4mhg-(0.08+n×0.04)×(SBP-150) Mean change of DBP=-5.6mhg-n×1.8mhg-(0.09+n×0.04)×((DBP-90)	

Aging effect:

x4, x5 are two randomly drawn independently distributed standard normal variables. They are re-drawn each year.

The two following equations calculate the change in SBP and DBP based on the current value of SBP, DBP, change in BMI, gender, and race.

DBP_diff=0.2+Age*0.282913980+DBP*0.031328327+SBP*0.030871363+Age*SBP*(-0.000770741)+Age*DBP*(-0.003093990)+BMI_Diff*0.372137437+Female*(-0.379980806)+IsAfricanAmerican*0.567931842+2.5848*Temp_x5

SBP_diff=-34.7+Age*1.02313914+DBP*0.13180962+SBP*0.18569020+Age*SBP*(-0.00590678)+Age*DBP*(-0.00268753)+BMI_Diff*1.79346394+Female*0.52748318+IsAfricanAmerican*0.96762149+7.300000*Temp_x4+2.505755*Temp_x5

SBP_diff: change in SBP

DBP_diff: change in DBP

Age: current age

SBP: current SBP
DBP: current DBP
BMI_diff: future change in BMI

A3. Hypoglycemia (severe)

Anti-hyperglycemia treatment	Incidence rate	Comments
Intensive lifestyle (diet and exercise/weight loss)	None	
Metformin (one OAD/non-insulin med)	None	
Metformin + Sulfonylureas (two OADs/non-insulin meds)	0.004 event per person per year	Zoungas et al. (2010)
Add Basal insulin to OAD/non-insulin med	0.02 event per person per year	1. Event per patient per year, median 0; 4 events in 243 patients (1.7%) (Holman et al., 2007) 2. 0 severe event in LANMET study (Yki-Järvinen et al., 2006) 3. 0.03 event per patient per year (Bretzel et al., 2008)
Intensive insulin therapy	0.12 event per person per year	0.02-0.35 event per patient per year (Zammitt and Frier, 2005)

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Appendix B: Michigan Model for Diabetes – Cost Model

Table B1. Costs of complications for Michigan Model for Diabetes

Event and ongoing costs of complications for Michigan Model for Diabetes	2014 US dollars[b]		Sources
	Event	Ongoing	
Baseline cost[a]	NA	2,315	[1]
Retinopathy			
Nonproliferative retinopathy	103	103	[2]
Macular edema or proliferative retinopathy	1,101	103	[2]
Blindness	2,951	2,951	[3]
Nephropathy			
Microalbuminuria	437	437	[4]
Proteinuria	748	748	[4]
End-stage renal disease with hemodialysis	99,046	99,046	[5]
End-stage renal disease with renal transplant	138,071	44,331	[5]
Neuropathy			
Clinical neuropathy	511	511	[2]
Amputation	42,929	1,500	[2]
Cardiovascular disease			
Angina	8,282	2,139	[2]
Myocardial infarction	41,744	2,307	[2]
Percutaneous transluminal coronary angioplasty[c]	8,282	2,139	[2]
Coronary artery bypass graft[c]	60,685	2,307	[2]
Myocardial infarction with coronary artery bypass graft[c]	60,685	2,307	[2]
Congestive heart failure	34,635	7,620	[6]
Ischemic stroke	55,278	18,448	[2]
Acute metabolic complication			
Hypoglycemia requiring hospitalization	16,991	NA	[3]
Death, by age in years			
74 or younger	74,776	NA	[7]
75-84	60,778	NA	[7]
85 or older	41,156	NA	[7]

NA, not applicable.

[a]The baseline cost is the annual direct medical cost for a white man with type 2 diabetes and BMI of 30 kg/m^2 who is treated with diet and exercise and has no microvascular, neuropathic, or cardiovascular complications.

[b]Costs are expressed in year 2014 US dollars using the general Consumer Price Index to reflect inflation.

[c]According to the statements in 2 JACC papers, about one third of patients undergoing PCI in the US have diabetes (see page e83 in the attached File 1) and about 35% of CABG patients have diabetes (see page e167 in the attached File 2). Also, according to a recent Circulation paper, it was estimated that in 2010, in the US, 492,000 patients underwent PCI while 219,000 underwent CABG (see page e275 in the attached File 3). With calculations using these data, what we could have is: The estimated number of diabetic patients treated with PCI in 2010 in the US would be 164,000 (=492,000*1/3), while that treated with CABG would be 76,650 (=219,000*0.35). Thus, based on these 2 calculated numbers, we could get that about 68% of diabetic patients who need the coronary revascularization procedures may use PCI, while 32% of them may get CABG.

References

1. Brandle M, Zhou H, Smith BR, et al. The direct medical cost of type 2 diabetes. Diabetes Care 2003;26:2300-4.
2. Based on Table 2 in the following study, the ongoing costs for retinopathy-related complications (except blindness) were assumed to be $75 in 2000 US$, and the event cost for nonproliferative retinopathy was assumed to be the same as the ongoing cost: O'Brien JA, Patrick AR, Caro J. Estimates of direct medical costs for microvascular and macrovascular complications resulting from type 2 diabetes mellitus in the United States in 2000. Clin Ther 2003;25:1017-38.
3. Ward A, Alvarez P, Vo L, Martin S. Direct medical costs of complications of diabetes in the United States: estimates for event-year and annual state costs (USD 2012). J Med Econ 2014;17:176-83. (Ward et al. followed the same approach as O'Brien et al.'s article published in Clin Ther 2003;25:1017-38, but the reasons for the higher cost of hypoglycemia requiring hospitalization reported by Ward et al. may include: (1) Ward et al.'s data was from year 2010, while O'Brien et al. used 1998 data and thus inflation for these many years won't reflect the increment on hospitalization cost for these many years; (2) inpatient physician resource-use profile, inpatient physician fee, and post-acute care cost may have been different between 1998 and 2010; for example, the physician fees applied in the O'Brien et al.'s analysis were much more lower, and definitely the hospital stay costs have changed a lot between these two analyses; (3) cost-to-charge ratios were different – 0.61 used by O'Brien et al. vs. 0.231-0.767 used by Ward et al.; and (4) there has been a minor change in the definition of the cases.)
4. Based on Table 3 in the following study, the ongoing costs were determined to be $396 in 2009 US$ for microalbuminuria and $678 ($396+$282) in 2009 US$ for proteinuria, and the event costs were assumed to be the same as the ongoing costs: Nichols GA, Vupputuri S, Lau H. Medical care costs associated with progression of diabetic nephropathy. Diabetes Care 2011;34:2374-8.
5. Based on Tables K7, K9, and K11 in the following report: U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.
6. Based on Table 2 in the following study, the event costs were derived from averaging total costs at 0-1 year in the incident heart failure cohort, and the ongoing costs were derived from averaging each of yearly total costs between year 1 and year 5 in the incident heart failure cohort: Liao L, Jollis JG, Anstrom KJ, et al. Costs for heart failure with normal vs reduced ejection fraction. Arch Intern Med 2006;166:112-8.
7. These data were from email consultation with Dr. Christopher Hogan on March 19, 2015, who is the president of Direct Research, LLC in Vienna, VA. These costs of death were the incremental per capita medical payments between the diabetes survivors in 2012 (costs in the year of 2012) and the diabetes decedents in 2012 (costs in the last 12 months of life) who were Medicare fee-for-service beneficiaries with Part A and Part B enrollment and with any diagnosis of diabetes on any physician or hospital (inpatient or outpatient) claims in 2011 and 2012.

Appendix C: Michigan Model for Diabetes – Utility Model

Table C1. Penalty functions for QWB-SA health utility scores

Disease status	Complication Level	QWB-SA Penalty
	Intercept	0.689
Sex	Male	(Ref)
	Female	-0.038
BMI (kg/m^2)	Obese (BMI ≥30)	-0.021
Diabetes Intervention	None or diet only	(Ref)
	Oral/non-insulin antidiabetic agents	-0.023
	Insulin	-0.034
Retinopathy	Both eye are not blind	(Ref)
	Non-proliferative retinopathy	-0.000
	Macular edema or proliferative retinopathy	-0.000
	Blind in one eye	-0.043
	Blind in two eyes	-0.170
Nephropathy	No nephropathy	(Ref)
	Microalbuminuria or proteinuria	-0.011
	ESRD dialysis	-0.078
	ESRD transplant	-0.078
Neuropathy	No neuropathy	(Ref)
	Clinical neuropathy	-0.065
	Amputation	-0.105
Cerebrovascular disease	No history of stroke	(Ref)
	History of stroke	-0.072
Cardiovascular disease	No CHD	(Ref)
	Angina	-0.026[†]
	MI/PTCA/CABG	-0.026[†]
	CHF	-0.052
High blood pressure	High BP or on BP medication	-0.011

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

Reference:

1. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH: Valuing health-related quality of life in diabetes. Diabetes Care 25:2238–2243, 2002
2. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans. Diabetes Care 35:2250–2256, 2012

Appendix D: Python Expressions Used in IEST

Expressions include mathematical and logical formulas. Expressions can be as simple as 1+2; they can use another parameter as in Age +1; They can be complex expressions using mathematical functions as in Exp(-Age); They can also use "if" statements as in Iif(Gr(Age+1,50),1,0); These expressions can also represent tables as in Table(1,3,0,0.5,1,Age,NaN,20,30,40) . These formulas may contain, as literals parameter names (including parameters that hold values, parameters that specify user defined functions, state indicator names, and some reserved words), mathematical operators, system built in functions. Below is a list of allowed operators:

D1. Supported arithmetic functions

- **+** : Addition operator
- **-** : negative/subtraction operator
- * : multiplication operator
- / : division operator (note that integers will be treated as floating point numbers)
- ** : power operator

D2. Other supported literals

- **()** : Parenthesis to determine the order of the calculation
- **[,]** : brackets enclosing comma separated values describe vectors and matrices. Note that this type of expression is limited to defined vectors and matrices

D3. Comparison operators

- **Eq(x1,x2)**: will return 1 if x1=x2 and 0 otherwise
- **Ne(x1,x2)**: will return 1 if x1<>x2 and 0 otherwise
- **Gr(x1,x2)**: will return 1 if x1>x2 and 0 otherwise
- **Ge(x1,x2)**: will return 1 if x1>=x2 and 0 otherwise
- **Ls(x1,x2)**: will return 1 if x1<x2 and 0 otherwise
- **Le(x1,x2)**: will return 1 if x1<=x2 and 0 otherwise

D4. A list of Boolean operators

In the following Boolean operators, the results are either 1 or 0. Any argument that not zero is considered be true and zero is treated as false.

- **Or(x1,x2,x3…)**: will perform a Boolean OR operation on two or more inputs
- **And(x1,x2,x3…)**: will perform a Boolean AND operation on two or more inputs
- **Not(x)**: will perform a Boolean Not operation on a single input
- **IsTrue(x)**: will return 1 for a numeric x that is not 0. Will return 0 otherwise.

D5. Mathematical functions

- **Exp(x)**: exponential
- **Log(x,n)**: logarithm of base n
- **Ln(x)**: natural logarithm
- **Log10(x)**: decimal logarithm

- **Pow(x,n)**: power operator similar to **
- **Sqrt(x)**: square root operator similar to **0.5
- **Pi()**: the mathematical constant approximately equal to 3.14159
- **Mod (x,n)**: Modulus of base n
- **Abs(x)**: Absolute value of x
- **Floor(x)**: closest integer equal to or below x
- **Ceil(x)**: closest integer equal to or above x
- **Max(a1,a2,a3…)**: the maximum value in the list
- **Min(b1,b2,b3…)**: the minimum value in the list

D6. Random number generators

These random functions can be used to define the distribution of parameters:

- **Bernoulli(p)**
- **Binomial(n,p)**
- **Geometric(p)**
- **Uniform(a,b)**: the arguments a and b define the lower and upper limits of the interval
- **Gaussian(mean,std)**

D7. Cumulative distribution functions

The last argument x represents a number for quantiles.

- **Bernoulli(p,x)**
- **Binomial(n,p,x)**
- **Geometric(p,x)**
- **Uniform(a,b,x)** the arguments a and b define the lower and upper limits of the interval
- **Gaussian(mean,std,x)**

D8. Control

- **Iif(Statement,TrueResult,FalseResult)**: Returns TrueResult if Statement is not 0, FalseResult if Statement is 0.

D9. Table

- **Table (TableParameters)**: A multi-dimensional table.

  TableParameters are provided as a string of comma-separated values. The Table input argument pattern is:

  D, N_1,…, N_D,V_1...$V_{(N1*N2*...*ND)}$, M_1, R_{10}...R_{1N1}.....M_D,R_{D0}...R_{DND}.

  - D: number of dimensions
  - N_1,… N_D: dimension size for dimension 1 to D
  - V_1...$V_{(N1*N2*...*ND)}$: table values
  - M_1,… M_D: dimension names for dimension 1 to D
  - R_{i0},…R_{iNi}:
    - If the dimension is discrete, define R_{i0}=NaN.

R_{i1}, … R_{iNi}: values for each level in the ith dimension

- If the levels dimension is continuous, the levels of each dimension are defined by cutpoints which represent the lower and upper bounds for each interval.
  R_{i0}: the lower bound of the first interval
  R_{i1}: the upper bound of the first interval and the lower bound of the second interval
  R_{iNi}: the upper bound of the N_ith interval

An example: The following table can be stored in the system with the expression
Table(2,2,3,1,2,3,4,5,6, Gender, NaN,0,1, Age,0,30,60,120)

	0<Age<=30	**30<Age<=60**	**60<Age<=120**
Gender=0	1	2	3
Gender=1	4	5	6

D=2: this is a 2 dimensional table
N1=2: the dimension size is 2 for the first dimension
N2=3: the dimension size is 3 for the second dimension
M1=Gender: the dimension name is “Gender” for the first dimension
M2=Age: the dimension name is “Age” for the second dimension
R_{10}=NaN: the Gender dimension is nominal
R_{11}=0: the value for the first level in the Gender dimension is 0
R_{12}=1: the value for the first level in the Gender dimension is 1
R_{20}=0: the lower bound of the first interval in the Age dimension is 0
R_{21}=30: the upper bound of the first interval and the lower bound of the second interval in the Age dimension is 30
R_{22}=60: the upper bound of the second interval and the lower bound of the third interval in the Age dimension is 60
R_{23}=120: the upper bound for the third and last interval in the Age dimension is 60.

D10. Special math symbols

Note that these may be platform dependent. Boolean operators treat NaN (Not a Number) as false as well as any other non-number type such as a vector/matrix.

- **Inf, inf**: will be recognized by the system as infinite. This symbol is not to be used in mathematical calculations as it may generate error. It can be used for bound checks for parameters.
- **NaN, nan**: will be recognized by the system as not a number. Note that comparison of NaN to any number including NaN will return False. Arithmetic operations using NaN produce NaN and may raise errors and therefore should be avoided.

Note that missing values are not supported by the system. An exception is population data upload in which case missing data values are ignored by default in simulation.