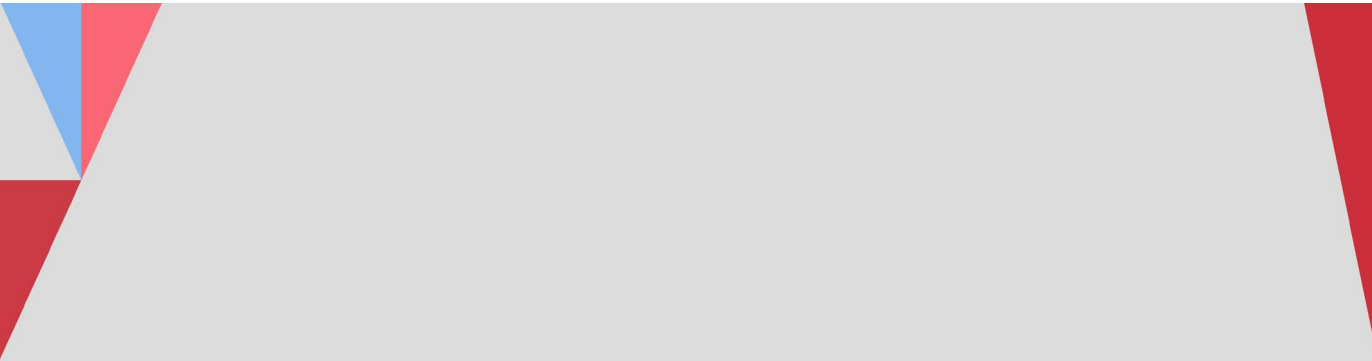


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The societal impact of early intensified treatment in patients with type 2 diabetes diabetes mellitus

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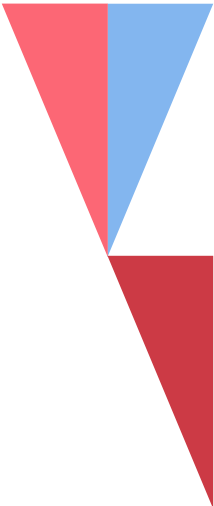
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List of Abbreviations

ADA	American Diabetes Association
CI	Confidence Intervals
DDD	Defined Daily Dose
DSA	Deterministic Sensitivity Analysis
HBA1C	Hemoglobin A1c
HF	Heart Failure
IDF	International Diabetes Federation
MI	Myocardial Infarction
MXN	Mexican Pesos
OECD	Organization for Economic Cooperation and Development
PSA	Probabilistic Sensitivity Analysis
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SI	Societal Impact
SU	Sulfonylureas
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	UK Prospective Diabetes Study
USD	US dollars
VBA	Visual Basic for Applications
VERIFY	Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes
WHO	World Health Organization
WPAI	World Productivity and Activity Impairment





1 Introduction

1.1 About this document

WifOR Institute, in conjunction with Novartis, has developed a societal impact (SI) model to estimate the societal value of early intensified treatment in type 2 diabetes mellitus (T2DM). The model adopts a societal perspective in Mexico, as the pilot country.

This user's guide provides step-by-step instructions for using the economic model. This hybrid technical document and user-guide details the design, structure and input parameters of the model designed to estimate the SI of early intensified treatment in T2DM, alongside guidance on user interaction.

1.2 Background

Diabetes is a major public health problem that imposes a serious burden on individuals and on society. It ranks among the most serious chronic diseases, with high risks for multi-system complications, such as heart disease, stroke, high blood pressure, blindness, kidney damage, nervous system disease, and lower-limb amputations [1]. There are enormous personal and societal costs associated with uncontrolled diabetes in terms of complications, patient quality of life, and health care system resources.

The term "diabetes mellitus", or simply "diabetes", describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs [2].

There are two main types of diabetes:

- Type 1 diabetes mellitus (T1DM) usually develops in childhood and adolescence; patients require lifelong insulin injections for survival.

- T2DM usually develops in adulthood and is related to obesity, lack of physical activity, and unhealthy diets. This is the more common type of diabetes and treatment may involve lifestyle changes and weight loss alone, oral medications or even insulin injections.

T2DM is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for suffering from severe complications, or death. T2DM risk factors include a complex combination of genetic, metabolic, and environmental factors, such as ethnicity, family history/genetic predisposition, obesity, low physical activity, and an unhealthy diet.

According to the recommendations by the American Diabetes Association (ADA) [3], the pharmacologic therapy for T2DM, metformin is the preferred initial pharmacologic agent which should be continued as long as it is well-tolerated and not contraindicated. Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. This was demonstrated by the VERIFY (Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes) trial [4] where initial combination therapy was superior to sequential addition of medications for extending primary and secondary failure. A patient-centred approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycaemia risk, impact on weight, cost, risk for side effects, and patient preferences.

Early intensified treatment has been previously shown to decrease the risk of T2DM complications. The UK Prospective Diabetes Study (UKPDS) [5], a large study that run for 10 years, demonstrated substantially decreased risk of microvascular complications in T2DM patients receiving early intensified treatment with either sulphonylureas (SUs) or insulin. A continued reduction in microvascular risk and emergent risk reductions for myocardial infarction (MI) and death from any cause were observed during 10 years of post-trial follow-up [6].

The Latin American Diabetes Association [7], including medical associations of 17 Latin American countries and Mexico, in its consensus statement for the management of hyperglycaemia recognises the importance of early, intensive glycemic control on long-term rates of microvascular complications, as it has shown by the UKPD studies.



2 Model Summary

2.1 Modelling objective and perspective

The objective of this project was to develop a SI model that could be used by Novartis to evaluate the societal implications of early intensified treatment when compared against late treatment intensification in various settings, using data from the Novartis VERIFY clinical trial. The core economic model was populated with data for Mexico. However, the model was designed to be easily adaptable to other countries.

The SI model was designed to consider, from a Mexican societal perspective, the clinical benefits, societal value, and associated direct medical costs related to the use of early intensified treatment in T2DM.

2.2 Modelling scenarios

For a given population, the current model evaluates the SI, the complication costs, and the drug acquisition costs under two scenarios:

- The stepwise approach: Reflects the management of T2DM with late intensified treatment. That is, patients starting treatment with metformin monotherapy until the 1st treatment failure. Then they transit to a combination therapy of metformin plus vildagliptin until they experience a 2nd treatment failure.
- The early intensified treatment approach: Reflects the management of T2DM patients with early intensified treatment. That is, patients starting treatment with combination therapy. In the model, combination treatment is defined as metformin plus vildagliptin as per the VERIFY clinical trial. When patients experience a 1st treatment failure, they remain in the same treatment pattern (i.e., they continue to receive combination therapy) until they experience a 2nd treatment failure.

Due to lack of country-specific data at the time conducting the study, we formulate a working hypothesis. That is, patients in both scenarios are assumed to receive insulin (40%) or SUs (60%) after a 2nd treatment failure.



In the VERIFY study [4], the primary endpoint was a 1st treatment failure event, and it was defined as having Hemoglobin A1c (HbA1c) levels at least 7% at two consecutive scheduled 13 weeks apart of randomization. One of the secondary endpoints in the clinical trial was the 2nd treatment failure, which represents the progression of HbA1c after experiencing a 1st treatment failure assessed by threshold (HbA1c being at least 7%). In accordance with the VERIFY study, treatment failure is defined as loss of glycemic control, i.e., not maintaining HbA1c levels below 7%.

2.3 Model structure

Figure 1 illustrates the schematic individual level simulation model structure that depicts the health states and allowable transitions included in the model.

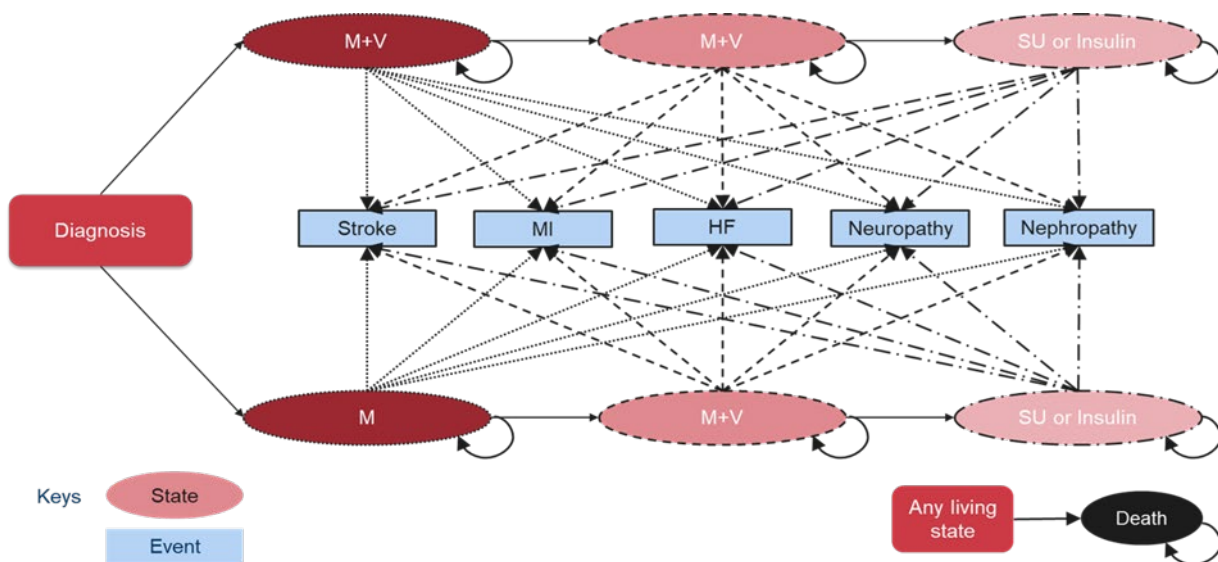


Figure 1: Schematic representation of the individual level simulation model

3 Getting started

3.1 Model navigation

The SI model was developed and implemented in Microsoft® Excel 365 for Windows.

The model can be navigated in three ways, depending on the user's preference:

- The user may simply use the worksheet tabs at the bottom of the screen to move to the desired worksheet (Figure 2)
- Alternatively, the user may use the Introduction worksheet (Figure 3). When the model opens, the “Table of contents” worksheet, is automatically displayed.
- The user may also navigate to the “Table of contents” and to the “Results” worksheets, from every spreadsheet in the excel via the use of the two respective buttons as shown in Figure 4.



Figure 2: Worksheet navigation | Worksheet tabs

	A	B	C	D	E	F
12		1	Introduction			
13		2	Model Structure	Overview		
14						
15		3	Results			
16		4	Graphs			
17		5	DSA simulation	Results and Sensitivity Analyses		
18		6	PSA simulation			
19						
20		7	Settings			
21		8	Clinical inputs			
22		9	Event probabilities			
23		10	Socioeconomic inputs			
24		11	Employment characteristics	Data inputs		
25		12	1st treatment failure			
26		13	2nd treatment failure			
27		14	death rates			
28		15	sim age-gender distribution			
29		16	Engine M-V			
30		17	Engine M-E			
31		18	Engine M-V single patient			
32		19	Engine M-E single patient			
33		20	Health Outcome_Population	Model calculations		
34		21	Health Outcome_Single Patient			
35		22	Societal Impact_Population			
36		23	Societal Impact_Single Patient			
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Figure 3: Worksheet navigation | “Table of contents” hyperlinks

The Societal Impact of early intensified treatment in type 2 diabetic patients

Introduction

Table of content

Results

Figure 4: Worksheet navigation | Buttons for “Table of contents” and “Results”

4

Changing model parameters

Four worksheets include country specific information that should be adapted with respect to the target country. These include: “**Settings**”, “**Clinical inputs**”, “**Socioeconomic inputs**”, and “**Death rates**”.

4.1 Cell types

Country-dependent
parameter

Country specific user-input cells with default data that user can adjust by manually entering new data.

No adaptation is needed

Input cells with default data that no adaptation is needed

Cells highlighted in light-yellow represent country-specific data, thus they should be adjusted accordingly. On the contrary, cells highlighted in light grey reflect non-modifiable inputs. These cells may contain no country-dependent data, or parameters automatically updated when the user adjust the country dependent cells. **Thus, the user is expected to modify only the light-yellow cells.**

Column C in the “Clinical inputs” and “Socioeconomic inputs” worksheets contains the base case inputs. This means that in a deterministic mode¹ these values will be used in the model.

In the “Clinical inputs” worksheet, columns D: Q were designed to facilitate the sensitivity analyses. Specifically, in column D the Standard Error (SE) is calculated, only for the input values that will be varied. Column I (the Live values) are designed to control for the base case and the sensitivity analyses mode. The model is by default set to deterministic mode².

Similarly, in the “Socioeconomic inputs” worksheet, column C contains the base case, and column D:G contain information and auxiliary calculations for the Deterministic Sensitivity Analysis (DSA).

¹ Deterministic models assume that no randomness is involved, in simple words the models are evaluated at the mean values of the input parameters. The purpose of probabilistic models is to reflect uncertainty around the input parameters of the decision model. To capture this uncertainty the analyst, specify appropriate statistical distributions for the input parameters to obtain a range of inputs and outputs.

² If the user desires to view the results in a probabilistic mode, this can be done by changing the cell C16 in the “Settings” worksheet from 0 to 1. Back in the “Clinical inputs” worksheet (and provided that the cell C16 is set to 1) by pressing <F9>, inputs in column I are updated to new parameters, only for the inputs that are programmed to probabilistically varied. The results will automatically change. The user can return to the deterministic mode, i.e., use the base case inputs by simple return the value 0, in cell C16 in the “Settings” worksheet. For Novartis purposes we recommend that the value in cell C16 is always switched to 0, reflecting the base case.



In the “Death rates” worksheet, only cells H9:H23 and cells K9:K23 should be adapted with country specific parameters. The cells refer to specific age and gender subgroups.

The user should only adapt cells in column C in the “Settings”, “Clinical inputs”, “Socioeconomic inputs” worksheets. The remaining cells are designed to be automatically updated.

In the “Death rates” worksheet, the user should only adapt columns H and K. The remaining cells are designed to be automatically updated.



5

Model worksheets

The below sections summarize the content of the excel worksheet, provide important information on the parameters used and on important calculations performed to facilitate the adaptation of the model.

5.1 Table of contents worksheet

The model's worksheets are grouped into four types as shown in Figure 3: **Overview, Results and Sensitivity analyses, Data inputs and Model calculations**. While most worksheets are accessible, making the model fully transparent to users and external audience, some worksheets do not need to be accessed in order to use the model.

- The **“Overview”** worksheets are two dark blue-coloured tabs. In these worksheets the user can view the general information of the model, Objective, Target Population, Intervention, Comparator, Time Horizon, Cycle Length, Model Overview and Model Outcomes.
- The **“Results and Sensitivity analyses”** worksheets are four red-coloured tabs; these present the results of our analysis. The worksheets include “Results”, “Graphs”, “DSA simulation” and “PSA simulation”.
- The **“Data inputs”** worksheets include nine green-coloured tables; these present all the inputs required for the model. The worksheets include “Settings”, “Clinical inputs”, “Events probabilities”, “Socioeconomic inputs”, “Employment characteristics”, “1st treatment failure”, “2nd treatment failure”, “Death rates”, “sim age-gender distribution”.
- The **“Model calculations”** worksheets include eight yellow-coloured tabs; these present the calculations of the individual level simulation and the population model, as well as the socioeconomic evaluation calculations. The worksheets include “Engine M+V”, “Engine M+P”, “Engine M+V single patient”, “Engine M+P single patient”, “Health outcome population”, “Health outcome Single Patient”, “Societal Impact population”, “Societal Impact Single Patient”. Please note, that the “Model calculations” worksheets, contain hidden formulas for the health and socioeconomic footprint and are password protected.

5.2 Overview worksheets

5.2.1 Introduction worksheet

This sheet informs the user about the main objectives of the study, target population, treatment strategies, model's time horizon, cycle length, model overview and the main outcomes.

5.2.2 Model structure worksheet

The worksheet contains one illustration to visualize the overall model structure (Figure 1). Moreover, general information regarding the succeeding steps undertaken in this model are explained.

5.3 Results and Sensitivity analysis worksheets

5.3.1 Results worksheet

5.3.1.1 Time horizon and discounting

Usually, diabetes models consider a lifetime time horizon. However, for the SI analysis this deemed inappropriate, as the parameters used to calculate the socioeconomic footprint (e.g., employment rates, wages, working hours) are susceptible and subject to highly unpredictable circumstances (e.g., financial recession).

The model was designed to report the analysis over a range of user-selected time horizons: 5 years, 10 years, and 15 years, which may be defined by the user in the “Results” worksheet via the use of the “Select time horizon” dropdown menu (Figure 5). Results are displayed cumulative over the defined time horizon. The analysis is conducted over a 10-year time horizon.

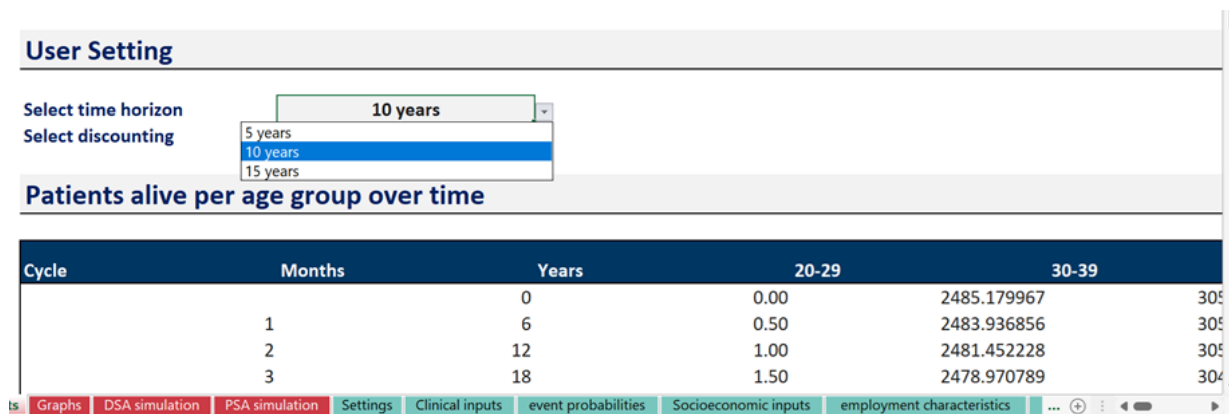


Figure 5: Selection of time horizon

The SI model has functionality to present estimates in the form of discounted values, via the optional application of discounting to future health, SI and costs. Discounting may be enabled or disabled in the “Results” worksheet, via the use of the “Select discounting” dropdown menu (Figure 6). More information about the discounting chosen as a model default are presented in chapter 5.4.1.



Figure 6: Control for discounting in the results

5.3.1.2 Base case results

In a nutshell, the “Results” worksheet presents the incremental difference in complication events, the incremental difference in working hours, the SI, the incremental difference in complication costs and the incremental difference in drug acquisition costs. Columns B: J contain information of the populated model (tables with the indication *a*, e.g., Table 1a), while R: Z contain information about a single patient (tables with the indication *b*, e.g., Table 1b).

- In cells B12:J42 there is information of patients alive in each age group and in each cycle. In this graph, the information is displayed until 15 years.
- Moving to cells B49:Z55 (**Table 1** of the Excel tool), the health footprint results are presented (i.e., the incremental difference in number of events between the two treatment scenarios). In these tables, the user can investigate the results per complication event

and per period one and two (as defined in the VERIFY clinical trial), and for insulin and SU separately. The “Gross Total for both genders” cells highlighted in light blue is the aggregated result.

- **Tables 2** in the Excel tool presents the incremental difference in working hours related to absenteeism.
- **Tables 3** in the Excel tool presents the incremental difference in working hours related to presenteeism.
- **Table 4** in the Excel tool presents the incremental difference in working hours related to no return to work, and
- **Table 5** in the Excel tool presents the incremental difference in working hours related to activity restriction ³.

The above tables provide information per complication, Period 1, Period 2, Insulin and SU. Moreover, results are presented separately for each gender.

- **Tables 6 and 7** in the Excel educational tool, demonstrate the summary of results per gender and per productivity parameter. Table 6 also provides information about each productivity parameter assessed (absenteeism, presenteeism, no return to work, activity restriction) separately, while table 7 show aggregated results for paid and unpaid work. Notably, paid work includes absenteeism, presenteeism and no return to work, while unpaid work includes activity restriction. The “Gross Total for both genders” is presented in light blue in both Tables 6 and 7.
- The incremental difference in working hours is subsequently monetized. In a similar way to the above, this is demonstrated in **Tables 8,9,10,11** in the Excel Tool. Table 11 provides information on the **Total societal impact** of early intensified treatment in patients with T2DM, and it is highlighted with light blue.
- Additionally, the model provides information about direct medical costs, namely the incremental difference in number of complication costs (**Table 12** in the Excel educational tool), and the incremental difference in drug acquisition costs (**Table 13** in the Excel educational tool).

This worksheet is a password protected sheet.

5.3.2 Graphs worksheet

The “Graphs” worksheet visualizes key methodological aspects and results. Specifically:

- **Graph 1** visualizes the share of an average patient in each treatment state. Time spent in the “no treatment failure” state is comparatively higher in the early intensified treatment group. In turn, the share of an average patient in treatment state, “1st treatment failure” and “2nd treatment failure” is comparatively higher in the stepwise approach group. That means, patients with early treatment intensification stay comparatively longer in the no

³ Activity restriction is related to unpaid work.



treatment failure state whereas patients in the stepwise approach experience faster a 1st and 2nd treatment failure.

- **Graph 2:** This graph visualizes the calculated 6-month complication event probabilities in the “no treatment failure” state (which represents Period 1), in the “1st treatment failure” state (which represents Period 2), and after the “2nd treatment failure” state (which is reflected by the use of insulin or SUs). For more information about the event probabilities the user is advised to refer to chapter 5.4.3.
- **Graph 3:** This graph visualizes the share of patients in each age and gender subgroup.
- **Graph 4:** This graph visualizes the patients alive per age subgroup and overtime. The graph presents the result for 30 cycles (15 years).
- **Graph 5:** Graph 5, presents a visualization of the result of the health footprint per complication event.
- **Graph 6:** This graph, presents information derived from secondary literature regarding the impairment of each complication event for three productivity parameters; absenteeism, presenteeism and activity restriction.
- **Graph 7:** This graph visualizes the aggregated incremental difference in working hours for paid and unpaid work per gender subgroup.
- **Graph 8:** Similarly, to the previous graph, Graph 8, presents the incremental difference in working hours. However, this graph shows the disaggregated results in terms of paid work. In other words, results for absenteeism, presenteeism, no return to work and activity restriction are displayed separately.
- **Graph 9:** The graph presents the monetized incremental difference in working hours per gender. This is the SI of early intensified treatment in T2DM patients.
- **Graph 10:** The first component of direct medical costs considered in this model, namely the complication costs, is presented in this graph.
- **Graph 11:** The second component of direct medical costs considered in this model, i.e., the drug acquisition costs, is presented in the graph.

5.3.3 DSA simulation worksheet

This subsection of the user's guide covers the general process of setting up one-way sensitivity analysis and advises the user on how to view and interpret the standard one-way sensitivity analysis graph presented in the “DSA simulation” worksheet.

A one-way Deterministic Sensitivity Analysis (DSA) is designed to test the sensitivity of the model results to uncertainty around model input parameters. When the DSA is run, the chosen parameters are varied individually to their predefined low and high values and the results are recorded and ranked based on the change they cause to the SI. The results of the DSA analysis are summarized in the form of a tornado chart. In the in the “Socioeconomic inputs” and “Clinical inputs” worksheet, the predefined low and high values are available in columns E and F

respectively. Column D, which includes the SE of the parameters represents an ancillary column. Ancillary cells are also the C119:E218 in the “Socioeconomic inputs” and cells C119:E123 in the “Clinical inputs” worksheet. In the left side of the “DSA simulation” worksheet, the user will see a tornado diagram similar to the figure below (Figure 7). In this figure, the results displayed are the parameters varied in the DSA. The bars in pink represent the variability in the SI associated with the upper bound input values; the bars in pink represent the variability in the SI associated with the upper bound input values. The inputs are in order from greatest change from the baseline SI to smallest change from the baseline SI, to give the appearance of a tornado. Therefore, the parameters in the beginning of the tornado diagram, are the parameters against which the model is most sensitive. On the other hand, the parameters that are associated with lower variability present the least sensitive variables of the model.

DSA is handled via Visual Basic for Applications (VBA); parameters varied in the DSA include the proportion of patients on the combination therapy, which can be found in the “Clinical inputs” worksheet. Moreover, all productivity parameters, weekly working hours and weekly activity hour⁴ are varied. These can be found in the “Socioeconomic inputs” worksheet along with relevant calculations.

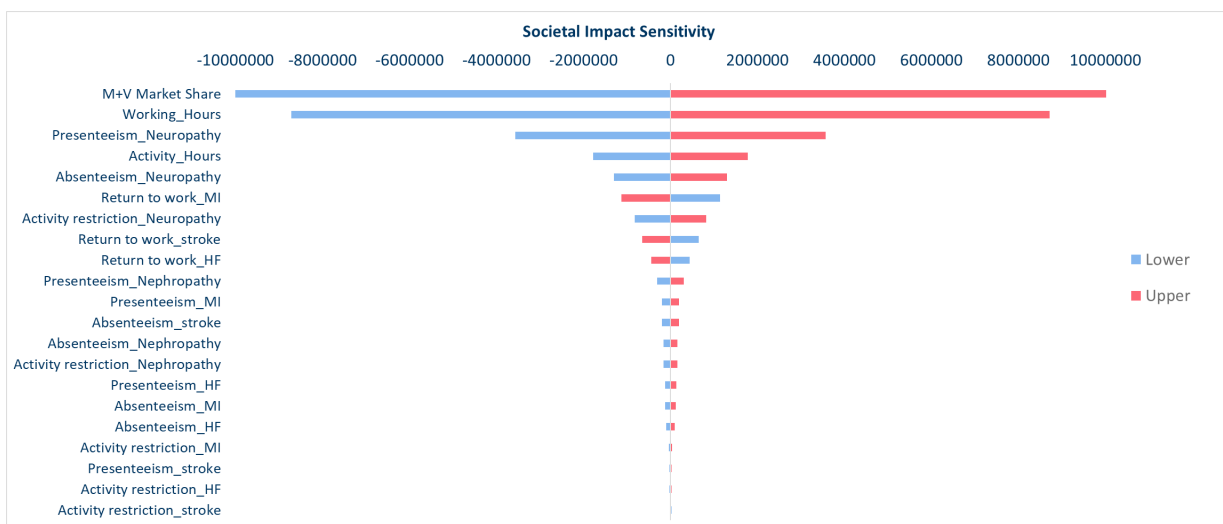


Figure 7: The tornado diagram

5.3.4 PSA simulation worksheet

A Probabilistic Sensitivity Analysis (PSA) is designed to consider how underlying uncertainty in model parameter values (typically defined and expressed in the model using confidence intervals (CI), SE, and assumed statistical distributions around the mean point estimate) can impact the model’s results. When the PSA is run, the model samples a value from the assigned distributions concurrently for all the key parameters. The model then runs the standard calculations and stores

⁴ Weekly activity hours are associated with unpaid work



the results as a single iteration set. The PSA repeats this process to build up a data set of relevant outcomes. This model is designed to run 1,000 iterations.

Parameters varied in the PSA, include the relative risk (RR) of diabetes mortality, event probabilities, complication costs and drug acquisition costs. These are all included in the “Clinical inputs” worksheet. Similarly with the DSA, next to base case inputs parameter, calculations required for a PSA are performed (K: Q).

The PSA results consist of the average of these 1,000 iterations and are shown in the cells BD8:BI8 in the “PSA simulation” spreadsheet. The Standard Deviation (SD) of the mean is shown in cells BD9:BI9. Below the PSA results, the user will see a dot plot graph which visualize all 1,000-point iterations and the base case value as shown in Figure 8.

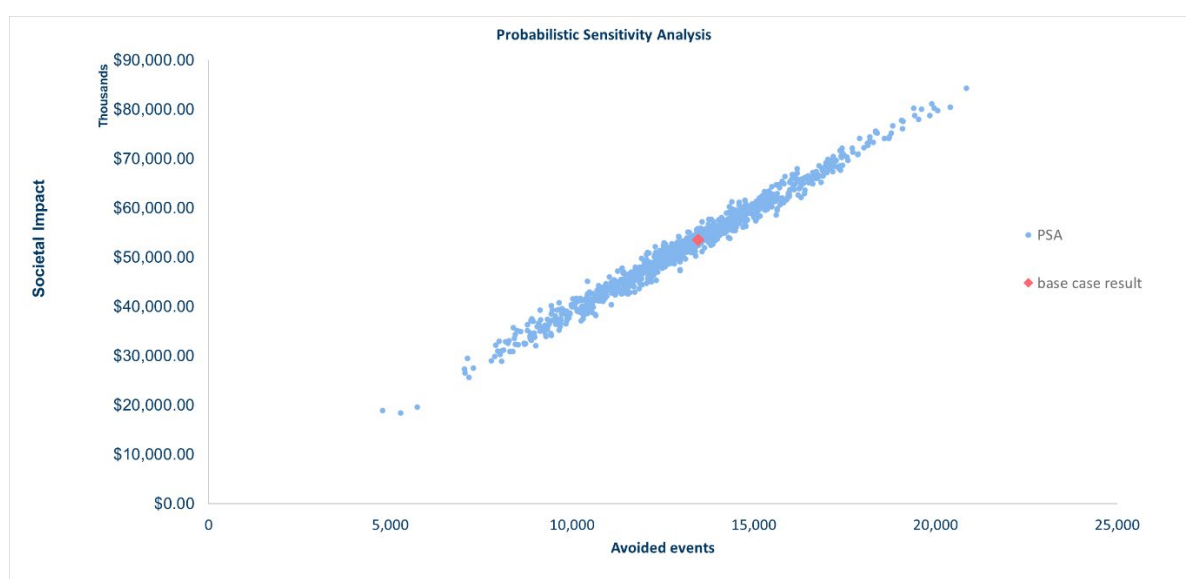


Figure 8: Probabilistic Sensitivity Analysis diagram

5.4 Data inputs

5.4.1 Settings worksheet

As a default model input, the SI model considers a 5% discounting value for both health outcomes and costs, as this is the current recommendation in Mexico and similar Latin America countries [8]. The user may adapt the discount rate, according to the target country, by manually overwrite the value in the “base case” cell (Cells C8 and C9) in the “Settings” worksheet (Figure 9). The lower and upper bound represents the lowest and the highest discounting values found in the literature [9].

The Societal Impact of early intensified treatment in type 2 diabetic patients

Settings

Table of content

Results

Keys

Country-dependent parameter

Country specific user-input cells with default data that user can adjust by manually entering new data. Enter the country specific inputs below

General model settings

Parameters	Base Case	Lower Bound	Upper Bound	Value
Discount rate outcomes	5.00%	3.00%	5.00%	5.00%
Discount rate costs	5.00%	3.00%	5.00%	5.00%

Days per year

Conventional SE (when data is not available)

365.25

10%

Probabilistic Sensitivity Analysis and Base Case control

PSA

0

Figure 9: Discount rate

As shown in Figure 9 in this worksheet, the model sets a conventional SE of 10%, to be used in the DSA and PSA.

Recommendation of possible sources for discount values

National recommendations of discounting differ between countries and over time. Furthermore, countries may have different discount rates for costs and health outcomes [10]. Usually, there is considerable variation of the rates used [10]. It is noteworthy that developing countries, may choose a relatively high discounting value [11].

5.4.2 Clinical inputs worksheet

This worksheet shows the default clinical, population and direct medical cost data. The user can change the default data by using the user-entry cells. The user-entry cells refer to the country-specific inputs to be adapted (column C). The user is advised to refer to chapter 6, for more information regarding the input cells that should be adapted.

5.4.2.1 Deriving the patient population

The target population is broadly defined as newly diagnosed T2DM patients, aged 20-69 years old. Within this population, evaluations may be performed considering various subgroups, stratified by age and gender with the following categories included:

- Males aged 20-29 years old
- Males aged 30-39 years old
- Males aged 40-49 years old
- Males aged 50-59 years old
- Males aged 60-69 years old
- Females aged 20-29 years old

- Females aged 30-39 years old
- Females aged 40-49 years old
- Females aged 50-59 years old
- Females aged 60-69 years old

The “Clinical inputs” worksheet contains parameters employed to derive the size of the evaluated population alongside information of the proportion of patients in each gender and age group. The model for the pilot country, assumes a hypothetical cohort of 10% receiving early intensified treatment (Figure 10). Due to lack of country-specific data, we built a working hypothesis that 10% of the patients will receive early intensified treatment with metformin plus vildagliptin. This input is country-specific; therefore, the user may modify the cell according to the target setting. However, if no country-specific data are available, the user may use the same assumption for other countries to form the hypothetical population for the model.

Population

Parameter	Base case
Country specific prevalence	14,123,200
Type 2 diabetes	90%
Diagnosed	52.50%
Treated	80.00%
No of patients on M+V	10.00%
Mean age	54.4
M+V_male_20-29	0.21%
M+V_male_30-39	2.60%
M+V_male_40-49	11.44%
M+V_male_50-59	18.21%
M+V_male_60-69	10.55%
M+V_female_20-29	0.25%
M+V_female_30-39	3.13%
M+V_female_40-49	13.76%
M+V_female_50-59	21.90%
M+V_female_60-69	12.69%

Treatment distribution post 2nd treatment failure

Parameter	Base case
SU	60.00%
Insulin	40.00%

Figure 10: Input parameters to populate the model and inputs for the treatment distribution among insulin and SUs after a 2nd treatment failure

Recommendation of possible sources for population parameters

In the core model, the prevalence of diabetes was derived from the International Diabetes Federation (IDF) Diabetes Atlas [12]. This database provides information for several countries including low- and middle-income countries. Evidence suggests that T2DM accounts for the 90% of all the diabetes cases[13]. Therefore, the model applies this rate to the overall diabetes prevalence to isolate those affected only from T2DM. The 90% may remain unchangable in many cases unless there are more precise data for the target country. Furthermore, it is well documented that diabetes may remain undiagnosed or untreated on a global scale and even in high income countries. Especially in low- to middle-income countries this aspect is particularly relevant[14]. In the model we apply a rate of 52.50% diagnosed diabetes patients [12]. Similar to prevalence, this value was derived from the IDF Diabetes Atlas. This database reports the proportion of people with undiagnosed diabetes (%) for several countries. To retrieve information regarding the proportion of untreated people a literature search should be conducted. The default value is a Mexico specific value.

5.4.2.2 Treatment distribution post 2nd treatment failure

The model assumes that after experiencing a 2nd treatment failure, patients could receive either insulin or SUs. Further, the model assumes 60% receiving SUs and 40% receiving insulin. Due to lack of country-specific data, we built this working hypothesis. These inputs are country-specific; therefore, the user may modify the cells according to the target setting. However, if no country-specific data are available, the user may use this assumption for other countries to form the hypothetical population for the model.

5.4.2.3 Relative risk of diabetes mortality

The model considers Mexico-specific 2019 age- and gender specific mortality rates, derived from statistical life tables [15] and account for the differential mortality hazard for those with a T2DM diagnosis compared to those without a diagnosis, by assuming a RR of 1.85 [16]. More details about age and gender specific death rates are provided in 5.4.7.

5.4.2.4 Event probability per cycle

Each treatment state includes the probability of experiencing complication events. Detailed information regarding the 6-month probabilities and how these were calculated are provided in



the 5.4.3. The diabetic complication events considered in the model include stroke⁵, MI⁶, heart failure (HF)⁷, neuropathy and nephropathy⁸.

5.4.2.5 Drug acquisition costs per cycle

This section of the worksheet sets out the default values for the drug costs in the model. Users may view and modify the cost profiles associated with each treatment strategy in the “Clinical Inputs” worksheet. Drug acquisition costs should be considered for metformin, metformin plus vildagliptin, metformin plus insulin and metformin plus SUs (Figure 11). All the calculated drug acquisition costs should be adjusted to reflect the cycle length i.e., 6 months. Patients in the VERIFY study, receive metformin in stable daily dose of 1000 mg, 1500 mg, or 2000 mg (either as monotherapy or combination therapy). The current model considers a parsimonious scenario where all patients receive a stable daily dose of 1000 mg. As default values, the model considers a cost dataset from Mexico.

Drug acquisition cost per cycle

Parameter	Base case	SE
M	\$36.70	\$3.67
M+V	\$235.76	\$23.58
M+Insulin	\$405.06	\$40.51
M+SU	\$72.17	\$7.22

Figure 11: Drug acquisition costs considered in the current model

The data are presented in USD and were taken from data on file from Novartis. The default values for drug acquisition costs in USD for Mexico are calculated based on the private market prices, as data on public market prices was not available at the time of the study implementation. First, we calculate the average daily cost for metformin and vildagliptin monotherapies (considering all listed and relevant medications in Mexico) using the provided pricing list by Novartis. Second, we compute the monthly costs for both and finally the 6-month costs to match our cycle length. In the combination therapy, the monotherapies costs were summed up. For insulin and SUs we use information on daily doses as per the Defined Daily Dose (DDD) [17]. According to the World Health Organization (WHO), “the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults” [17].

The user can change the default data by using the user-entry cells.

⁵ Stroke includes ischemic stroke and hemorrhagic stroke

⁶ MI includes MI and acute MI

⁷ HF includes HF, congestive HF and chronic HF

⁸ Nephropathy includes diabetic nephropathy



5.4.2.6 Complication costs

Complication costs for a given event were derived based on the specified event cost and the number of avoided events arising from receiving early instead of late treatment intensification. Event costs included in the model were obtained from Hunt et al.[18]. Since the results of the analysis is designed to be reported in USD, all cost inputs should be converted to USD. Hunt et al. used the exchange rate in the year of the analysis to convert the 2011 Mexican Pesos (MXN) to 2015 USD. The model uses a similar approach by applying the US dollar-exchange rate in 2021 to the reported complication costs in MXN. Figure 12 provides information in the complication costs implemented in the model.

Recommendation of possible sources for population parameters

To retrieve information about the complication costs, a literature search was performed. Moreover, in several countries information on Diagnosed-Related Groups (DRGs) are available, containing reliable information about the costs to the healthcare system of several diseases.

Complication costs

Parameter	Base case	SE
Stroke	\$3,061.47	\$306.15
MI	\$3,073.52	\$307.35
Heart Failure	\$2,026.54	\$202.65
Neuropathy	\$1,859.19	\$185.92
Nephropathy	\$19,084.04	\$1,908.40

Figure 12: Complication event costs considered in the current model

5.4.2.7 Sensitivity analysis related information in the Clinical inputs worksheet

Columns K to Q in the “Clinical inputs” worksheet set out the calculations required to perform a PSA. Parameters varied in the PSA include the RR of diabetes mortality, the event probabilities per cycle, the drug acquisition costs per cycle and the complication costs. Thus, the PSA calculations concern only these parameters. The user is not required to make any changes in the respective columns. Moving to cells C119:D123, there is an auxiliary one-way data table for the one-way DSA. Similarly, the user is not required to make any changes in any cell.

5.4.3 Event probabilities worksheet

Each treatment state includes the probability of experiencing complication events. The probability of experiencing complications while in the no treatment failure and 1st treatment failure related states is derived from patient level data of the VERIFY study for each treatment scenario, respectively [19]. The probability of experiencing complications after 2nd treatment failure (in SUs or insulin) was obtained from a real-world study [20]. The VERIFY clinical trial provides information on the complication event's 5-year incidence, while the real-world study reports the 6-year incidence. The conversion of the event probabilities to reflect the models cycle length was based on Briggs et al.[21] recommendations. These calculated probabilities are subsequently fed to the "Clinical inputs" worksheet, so they will inform the individual level simulation model. This is a password protected sheet.

5.4.4 Socioeconomic inputs

5.4.4.1 Productivity inputs

To determine the SI of early intensified treatment, an extensive literature review was conducted to identify and collect the productivity parameters for the selected complication events. The productivity parameters include:

- Absenteeism (i.e., being absent from work)
- Presenteeism (i.e., being present at work but with reduced work ability)
- Reduced labour force participation after complication events due to no return to work.
- Activity Restriction (i.e., reduced ability to perform unpaid work activities)

Recommendation of possible sources

The productivity parameters mentioned above, should be obtained for each complication (stroke, MI, HF, nephropathy and neuropathy). Usually, productivity impairment is quantified by questionnaires e.g., the Work Productivity and Activity Impairment questionnaire (WPAI). The above parameters should be obtained from the literature and are usually country specific. However, given the scarcity of relevant available data, default data could be used as an approximation for the adapted country.

5.4.4.2 Employment rates

To quantify losses due to poor health for the Mexican economy, we first determined the working time of an average Mexican employed person stratified by age and gender. As mentioned in section 5.4.2.1, the model considers 10 age and gender subgroups. Therefore, employment rates were captured and analysed for the respective subgroups. Considering age- and gender-specific cohorts in the defined target population for early intensified antidiabetes treatment enables us to model the socioeconomic effects in a precise manner.

Recommendation of possible sources

Information about the employment rates may be obtained by the National Statistical Office of a country. A challenge that may arise is that information for the employment rates may not be directly available for the specific age and gender subgroups. In this case, the obtained data should be adjusted accordingly. In cases where only average employment rate of a country exists with no subgrouping information, the average rate may be applied as an approximation.

5.4.4.3 Average weekly working hours

Similar to employment rates (chapter 5.4.4.2) to quantify the socioeconomic footprint we use information on the average weekly working hours of the general population in the country of interest. Since the model considers specific age and gender subgroups, inputs of weekly working hours should follow the same distribution or adapted properly to reflect the same subgroups.

Recommendation of possible sources

Information about the weekly working hours may be obtained by the National Statistical Office of a country. A challenge that may arise is that information for the weekly working hours may not be directly available for the specific age and gender subgroups. In this case, the obtained data should be adjusted accordingly. An another case would be that data report average daily hours working or average monthly hours working. This could be overcome by simple calculations to obtain weekly data (i.e., multiply by 5 the daily working hours assuming five working days during the week).

5.4.4.4 Average unpaid hours worked in a country

As discussed previously, and since we consider specific subgroups in our analysis, inputs of weekly unpaid working hours should follow the same distribution or adapted properly to reflect the same subgroups.

Information about weekly unpaid working hours is usually retrieved from time use surveys for the countries of interest. These surveys are usually available from country's official statistical



authorities. Default data in this model considers inputs for the Mexican population and the following unpaid activities has been considered:

- Unpaid domestic work for own household
(Food preparation and service of food; house cleaning; cleaning and care of clothing and footwear; maintenance, installation, and minor repairs of the dwelling and other household goods; shopping; payments and formalities; management and administration)
- Unpaid care work for household members
(Special care for chronically or temporarily ill or disabled members of the household; Care for household members from 0 to 5 years of age; Care for household members from 0 to 14 years of age; Care for household members 15 to 59 years old; Care for household members 60 years of age and older)
- Unpaid work as support to other households and voluntary work
(Domestic work; special care for chronically ill, temporarily ill or disabled persons from other households; Age-appropriate care of persons in other households; Voluntary and community unpaid work and community).

It is noteworthy that in different countries, the above categories may be differentiated. It is of great importance that unpaid activities would be differentiated from leisure time. Leisure time activities do not reflect possible activity losses and are excluded from the analysis.

Recommendation of possible sources

Information about the weekly unpaid working hours may be obtained by time use surveys. Time use surveys are conducted in several countries. These surveys are usually available through National Statistical Offices. A challenge that may arise is that information for the weekly unpaid hours may not be directly available for the specific age- and gender subgroups. In this case, the obtained data should be adjusted accordingly.

5.4.4.5 Working weeks/activity

To quantify the hours worked for our chosen 6 months cycle, the model needs to estimate the information about weekly paid and unpaid hours worked to reflect the cycle length.

Concerning paid work, this is done by first estimating the real working weeks in a time interval of 6 months. To do so, first the actual working days in a year need to be identified. This should exclude weekends and holidays. Subsequently, the actual number of working days are divided by 5 (assuming one working week corresponds to 5 days). The retrieved number is finally divided by 2 to get the working weeks for 6 months.

For the unpaid work we divide the total weeks in a year by 2, to get the number of weeks in 6 months. The assumption is that unpaid working activities could be performed anytime during the year, irrespectively of holidays or weekends (Figure 13).

Working weeks/ activity weeks per half of a year in country

Parameters	Base case
working weeks per 6 month	25.4
activity weeks per 6 month	26

Figure 13: Working and activity weeks per 6-months

5.4.4.6 Average hourly wage

Finally, to monetize the avoided productivity and activity losses, the model uses information about the average wage and the average minimum wage for a country in USD. The average wage in a specific country is used for the monetization of paid work, while the average minimum wage is used to monetize unpaid work. This information may be obtained from the National Statistical Offices or from other publicly available sources e.g., the OECD [22].

5.4.5 Employment characteristics worksheet

This worksheet contains information of a country's employment characteristics derived from the "Socioeconomic inputs" worksheet. The data include employment rates, weekly working hours and weekly activity hours per gender. However, in this worksheet data inputs are reported per age and not per age group to facilitate the Socioeconomic evaluation. This sheet informs the inputs used in the SI valuation. The user is not required to make any adaptation as the sheet is directly connected to the "Socioeconomic inputs" sheet. Thus, the inputs are automatically updated.

5.4.6 1st and 2nd treatment failure worksheets

The worksheets "1st treatment failure" and "2nd treatment failure" present the results of four independent survival analyses implemented in R version 4.0.5. Kaplan Meier estimates, as well as the parametrization of five standard parametric distributions are presented in separate tables. We use the survival analyses inputs to inform the probabilities of experiencing a 1st and 2nd treatment failure in each treatment arm. These probabilities are then used in the individual level simulation model. These are password protected worksheets.

5.4.7 Death rates worksheet

In this model, a diabetes adjusted death probability is applied. As previously stated, the described modelling was applied to five age groups. These subgroups also represent the age-dependant background mortality. The background mortality was derived from Mexican lifetables[15]. The life tables reported the per gender 5-year death probability in selected age groups. To calculate the 6-month probability of dying we again refer to the Briggs et al.[21] formulas.

As mentioned in chapter 5.4.2.3, further to the background mortality, a RR of increased mortality in T2DM population compared to the general population is applied.

5.4.8 Age and gender distribution worksheet

This worksheet contains parameters employed to derive the size of the evaluated population in each subcohort. The simulation is based on the the patient characteristics of the VERIFY study.

5.5 Calculations worksheets

The “Calculations” worksheets contain the calculation required to estimate the health and socioeconomic footprint.

- The worksheets “Engine M+V”, “Engine M+P”, “Engine M+V single patient”, “Engine M+P single patient” refer to the individual level simulation and population model calculations.
- The worksheets “Health outcome population” and “Health outcome single patient” refer to the incremental difference between the two treatment scenarios to obtain the result of the health footprint, i.e., the number of avoided events with early intensified treatment.
- The worksheets “Societal Impact population” and “Societal Impact single patient” by retrieving information from the incremental difference in number of events, i.e., from the “Health outcome population” and “Health outcome single patient” worksheets respectively, as well as socioeconomic inputs as defined in chapters 5.4.4 and 5.4.5, calculate the Socioeconomic footprint.

6 Running the analysis

This chapter of the user guide will provide an example of setting up a deterministic analysis using different input values from the default values the current model use. The user should note that the data inputs used for this example do not represent actual country values.

6.1 Adapt the user-input cells

We assume that in the new country the recommendation for the discount is 3%. The first step is to adapt the new value in cells C8:C9 (the base case cells). Cells F8:F9, are automatically updated with the new input value (Figure 14).

General model settings					
Parameters	Base Case	Lower Bound	Upper Bound	Value	
Discount rate outcomes	3.00%	1	3.00%	5.00%	3.00%
Discount rate costs	3.00%		3.00%	5.00%	3.00%
Days per year					365.25
Conventional SE (when data is not available)					10%
Probabilistic Sensitivity Analysis and Base Case control					
PSA		0			

Figure 14: Changing the base case in the discounting cells.

Subsequently we will apply relevant changes in the “Clinical inputs” worksheet (Figure 15 and 16). The only changes implemented concern the “base case” values. All the other cells change automatically.

Population					
Parameter	Base case	SE	Lower bound	Upper bound	Use value
Country specific prevalence	14,123,200				14,123,200
Type 2 diabetes	90%				90%
Diagnosed	52.50%				53%
Treated	80.00%				80%
No of patients on M+V	10.00%	0.01	0.08	0.12	10%
Mean age	54.4				54.4
M+V male 20-29	0.21%				0.21%
M+V male 30-39	2.60%				2.60%
M+V male 40-49	11.44%				11.44%
M+V male 50-59	18.21%				18.21%
M+V male 60-69	10.55%				10.55%
M+V female 20-29	0.25%				0.25%
M+V female 30-39	3.13%				3.13%
M+V female 40-49	13.76%				13.76%
M+V female 50-59	21.90%				21.90%
M+V female 60-69	12.69%				12.69%
Treatment distribution post 2nd treatment failure					
Parameter	Base case	Use value			
SU	60.00%	60%			
Insulin	40.00%	40%			

Figure 15: Changing the population and treatment distribution post 2nd treatment failure parameters

Drug acquisition cost per cycle

Parameter	Base case	SE
M	\$40.00	\$4.00
M+V	\$150.00	\$15.00
M+insulin	\$350.00	\$35.00
M+SU	\$60.00	\$6.00

3

Live value
\$40.00
\$150.00
\$350.00
\$60.00

Complication costs

Parameter	Base case	SE
Stroke	\$4,000.00	\$400.00
MI	\$2,000.00	\$200.00
Heart Failure	\$3,000.00	\$300.00
Neuropathy	\$2,000.00	\$200.00
Nephropathy	\$10,000.00	\$1,000.00

4

Live value
\$4,000.00
\$2,000.00
\$3,000.00
\$2,000.00
\$10,000.00

Figure 16: Changing the direct medical costs input values

Moving to the “Socioeconomic inputs” worksheet, for this work case, we will not modify the productivity input parameters, but we will adapt the employment rates, the weekly working hours, the weekly activity working hours and the wages as shown in the following figures (Figure 17 and Figure 18).

Employment rates in country

Parameters	Base Case	SE	Deterministic Sensitivity Analysis			Value
			Lower bound	Upper bound		
	1		0.1	0.804	1.196	3
employment rate_male_15-19	0.4					
employment rate_male_20-29	0.6					
employment rate_male_30-39	0.8					
employment rate_male_40-49	0.9					
employment rate_male_50-59	0.9					
employment rate_male_>60	0.45					
employment rate_female_15-19	0.2					
employment rate_female_20-29	0.6					
employment rate_female_30-39	0.7					
employment rate_female_40-49	0.65					
employment rate_female_50-59	0.58					
employment rate_female_>60	0.25					

5

Live value
1
0.4
0.6
0.8
0.9
0.9
0.45
0.2
0.6
0.7
0.65
0.58
0.25

Average weekly hours actually worked on the main job in country

Parameters	Base Case	SE	Deterministic Sensitivity Analysis			Value
			Lower bound	Upper bound		
	1		0.1	0.804	1.196	1
weekly working hours_male_1	20					
weekly working hours_male_2	50					
weekly working hours_male_3	55					
weekly working hours_male_4	56					
weekly working hours_male_5	42					
weekly working hours_male_>60	30					
weekly working hours_female_1	15					
weekly working hours_female_2	40					
weekly working hours_female_3	35					
weekly working hours_female_4	40					
weekly working hours_female_5	35					
weekly working hours_female_>60	28					

6

Live value
1
20
50
55
56
42
30
15
40
35
40
35
28

Figure 17: Changing employment rates and average weekly working hours

Average unpaid hours worked in country

Deterministic Sensitivity Analysis							Live value	
Parameters	Base Case	SE	Lower bound	Upper bound	Value			
		1	0.1	0.804	1.196			1
weekly activity hours_male_15	15							15
weekly activity hours_male_20	20							20
weekly activity hours_male_30	30							30
weekly activity hours_male_40	28							28
weekly activity hours_male_50	17							17
weekly activity hours_male_60	10							10
weekly activity hours_female_15	12							12
weekly activity hours_female_20	42							42
weekly activity hours_female_30	56							56
weekly activity hours_female_40	40							40
weekly activity hours_female_50	20							20
weekly activity hours_female_60	30							30

Working weeks/ activity weeks per half of a year in country

Parameters	Base case	Live value
working weeks per 6 month	25.4	25.4
activity weeks per 6 month	26	26

Average hourly wage in country

Deterministic Sensitivity Analysis							Live value	
Parameters	Base Case	SE	Lower bound	Upper bound	Value			
		1	0.1	0.804	1.196			1
average hourly wage	\$10.00						\$	10.00
hourly minimum wage	\$2.00						\$	2.00

Figure 18: Changing average unpaid hours worked and average hourly wage

Finally, the last worksheet to be adapted according to the targeted setting is the “Death rates” worksheet, which contains information about the background mortality in several age groups for both genders. In this worksheet, only cells H9:H23 and K9:K23 are to be changed (Figure 19). Likewise, all other cells in the spreadsheet will be automatically updated.

Death Probability	Age Group	Male	Converted	Converted	Female	Converted	Converted
Year 2019		Given	5 year rate	6 months probability	Given	5 year rate	6 months probability
Indicator		5 year probability			5 year probability		
nxq - probability of dying betw	15-19 years	0.001462899	0.000292794	0.000146396	0.000776035	0.000155268	7.7631E-05
nxq - probability of dying betw	20-24 years	0.002128563	0.000426166	0.000212856	0.000822443	0.000164556	8.22747E-05
nxq - probability of dying betw	25-29 years	0.002261149	0.000452742	0.000226149	0.00108491	0.0002171	0.000108544
nxq - probability of dying betw	30-34 years	0.003211624	0.000643358	0.000321162	0.001782118	0.000356742	0.000178355
nxq - probability of dying betw	35-39 years	0.0047863	0.000959558	0.00047863	0.002587811	0.000518233	0.000259083
nxq - probability of dying betw	40-44 years	0.007298755	0.001465104	0.000729875	0.000732284	0.000804575	0.000402207
nxq - probability of dying betw	45-49 years	0.011818328	0.002377744	0.00118183	0.006977269	0.001400345	0.000699927
nxq - probability of dying betw	50-54 years	0.020566998	0.004156289	0.002056698	0.011274292	0.002267666	0.00113319
nxq - probability of dying betw	55-59 years	0.034960024	0.007117151	0.003496002	0.019127861	0.003862633	0.001929453
nxq - probability of dying betw	60-64 years	0.058541155	0.012064929	0.006014306	0.031609602	0.006423994	0.003206844
nxq - probability of dying betw	65-69 years	0.086777693	0.018155187	0.009036317	0.047063477	0.009641397	0.004809098
nxq - probability of dying betw	70-74 years	0.127107661	0.027188611	0.01350232	0.075434554	0.015686288	0.007812467
nxq - probability of dying betw	75-79 years	0.18760994	0.041554937	0.020563104	0.112076107	0.023773848	0.011816554
nxq - probability of dying betw	80-84 years	0.302989961	0.072191093	0.03545187	0.215419261	0.048521164	0.02396866
nxq - probability of dying betw	85+ years	1	1	0.39346934	1	1	0.39346934

Figure 19: Changing background mortality inputs

6.2 Run the model

Once the user has changed the above parameter values, the model will automatically recalculate the health and socioeconomic footprint. That is, by navigating in the “Results” worksheet, the incremental difference in the number of avoided events, the Societal Impact and all other relevant results have automatically been updated. For example, see Figure 20, which represents the new result of the health footprint.

Incremental difference in no of events per treatment period | Population

Table 1a: Incremental difference in number of complication events	Period 1	Period 2	Both sexes		
	M+V	M+V	Insulin	SU	Total per complication
Stroke	1,098	466	197	296	2,058
MI	-1,255	1,945	1,234	444	2,368
HF	-5,396	1,549	2,093	2,672	918
Neuropathy	-7,181	3,227	6,848	5,322	8,216
Nephropathy	316	-927	729	1,244	1,361
Gross Total for both sexes	14,922				14,922

Figure 20: Healthfootprint result of the updated values

The specific output value is an undiscounting one, referring to 10 years. As mentioned in previous sections, the user by the dropdown menus in cells C6 and C7, can choose to view the discounted results for three-time horizons: 5, 10 and 15 years. Graphs, in the “Graphs” worksheet are automatically updated as well.

Unlike the base case analysis, for which the results are immediately available to the user, the one-way sensitivity analysis requires the user to run two VBA codes in the excel. By running these two VBA codes at a first step the user will:

- 1) Update the parameters in the one-way data tables. These could be implemented by just pressing the “One-way data tables” button in the “DSA simulation” spreadsheet.
- 2) Subsequently the user will run the DSA. This could be easily performed by pressing the “Run DSA” button in the same spreadsheet.

It could take up to 10 minutes to run both.

To run a PSA the user should simple press the “Run PSA” button. The user should notice that running a PSA could take up to 3 hours due to the large number of iterations.

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