Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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I. eMethods for modelling hepatitis C

1. Markov model details

The discrete stages of the Markov model in this analysis are shown in eFigures 1 and 2. For each treatment policy, patients are allocated to fibrosis stages F0 through F4 (eTable 1A) Patients are treated according to the policy at each fibrosis stage (eTable 1B and 1C). If the policy allows treatment at a selected fibrosis stage, the patients are allocated to treatment with one of the seven treatment options (plus no treatment) (eTable 1D) using treatment specific attributes related to cost, adverse events, efficacy and discontinuation probabilities. For patients entering therapy, they either achieve SVR or fail therapy depending on the treatment effectiveness probabilities. The model assumes that patients who discontinue or fail therapy are at risk of natural CHC progression and related complication, therefore, these patients transition into the natural history Markov states (the same fibrosis state in which they entered treatment but failed) and cycle through until death. Those who achieve SVR, transition into post-SVR Markov states and cycle through until death. Within the post-SVR states, the patients may regress to a better state of health, progress to a worse state or stay in the same fibrosis stage as the one in which they initiated treatment. The Markov model health states, progression and regression transition probabilities and proportions are derived from published literature.1-5 The Markov model cycles (either quarterly, half-year or full year) correspond to the duration of the therapy being analyzed. The cycle lengths for the seven treatments were as follow: quarterly for Sof/PR, SOF/LDV (8/12 weeks and 12 weeks); half-year for Sof/R, Sim/Sof, and 3D±R; and one-year for P/R and no treatment. For each cycle, the patients will accrue the corresponding costs and QALYs of the health state over a lifetime.

eTable 1. METAVIR Fibrosis Score, Treatment Policies for Evaluation, and Modeled Treatment Options

(A) METAVIR score for classification of liver fibrosis

Fibrosis Stage	Histological definition
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with rare septa
F3	Numerous septa without cirrhosis
F4	Cirrhosis (compensated)

(B) Decision analytic model – Treat All vs. treat at F3/F4with each of the seven therapy options

Policy	Description of policy
1	Treat Early – Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4)
2	Treat at F3/F4 – Wait and treat only when patients reach stages F3 and F4

(C) Decision analytic model – Treatment by Fibrosis Stage with each of the seven therapy options

Policy	Description of policy
1	Treat all – Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4)
2	Treat at F1 – Wait and treat only when patients reach stages F1, F2, F3 and F4
3	Treat at F2 – Wait and treat only when patients reach stages F2, F3 and F4
4	Treat at F3 – Wait and treat only when patients reach stages F3 and F4
5	Treat at F4 – Wait and treat only when patients reach stage F4
6	No Treatment – the cohort cycles through the model without treatment.

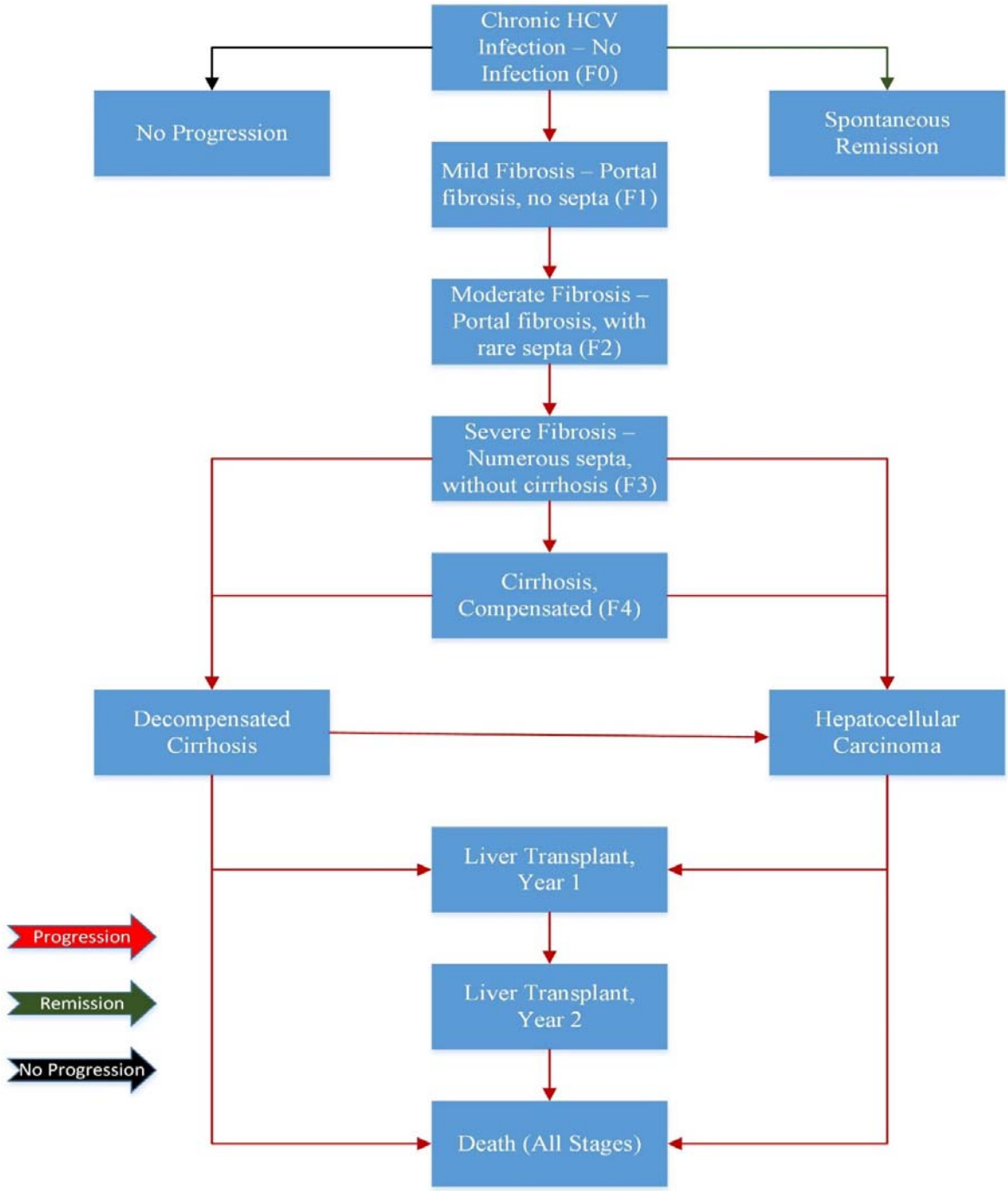
(D) Treatment options

Option	Treatment regimen	Treatment duration (weeks)
1	No Treatment	--
2	Peg-Interferon/Ribavirin (P/R)	48
3	Sofosbuvir + Peg-Interferon/Ribavirin (Sof/PR)	12
4	Sofosbuvir + Ribavirin (Sof/R)	24
5	Sofosbuvir + Simeprevir (Sim/Sof)	12/24*
6	Sofosbuvir + Ledipasvir (SOF/LDV (8/12))	8/12†
7	Sofosbuvir + Ledipasvir (SOF/LDV (12))	12
8	Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir (3D) ± Ribavirin‡	12/24‡

*F0-F3 – treatment duration is 12 weeks, F4 – treatment duration is 24 weeks.

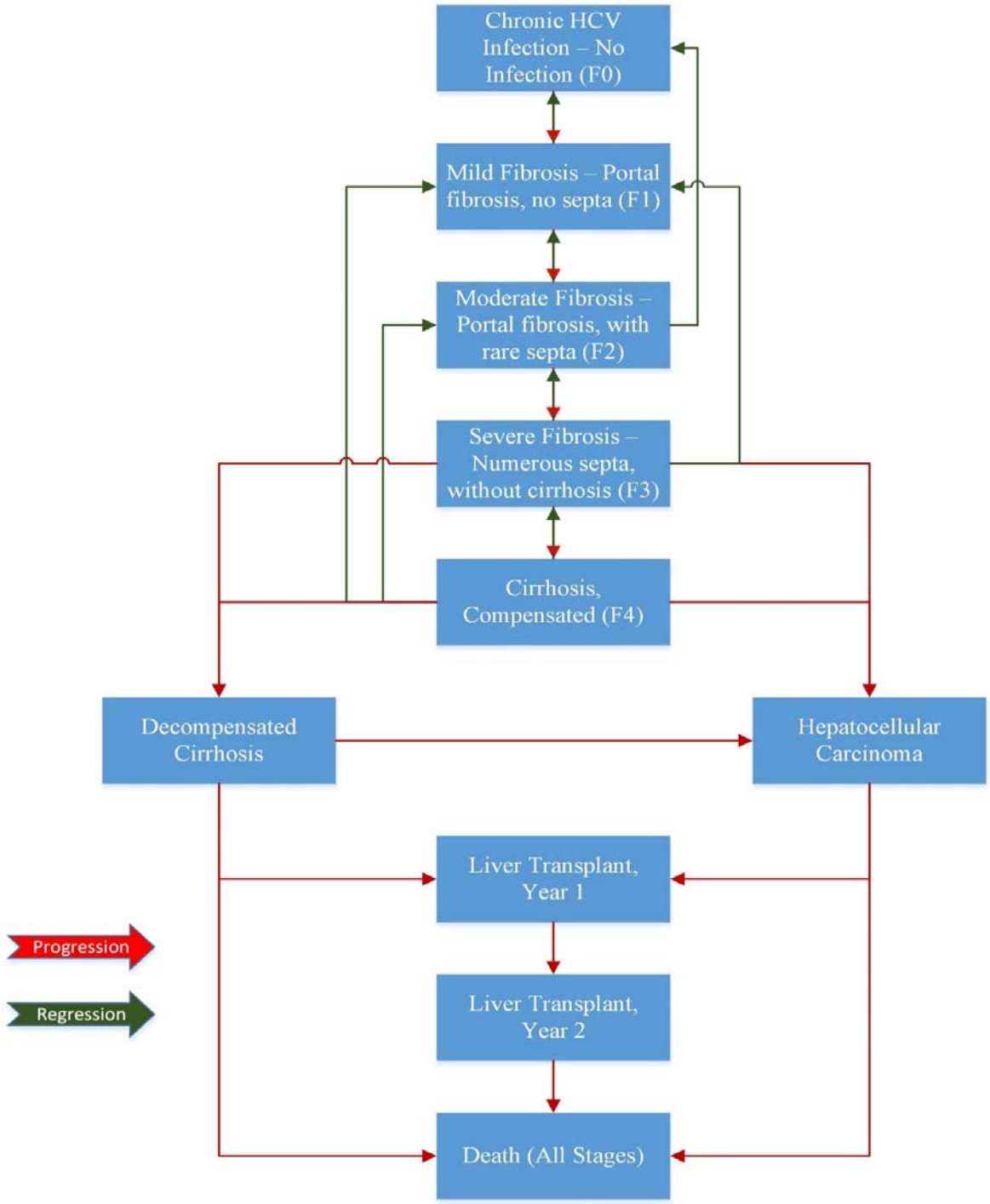
†Stages F0-F3 – treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks

‡Genotype 1a, F0-F3 – treatment duration is 12 weeks and Genotype 1a, F4 – treatment duration is 24 weeks – all *with* ribavirin. Genotype 1b, F0-F3 treatment duration is 12 weeks, *without* ribavirin; Genotype 1b, F4 treatment duration is 12 weeks, *with* ribavirin.



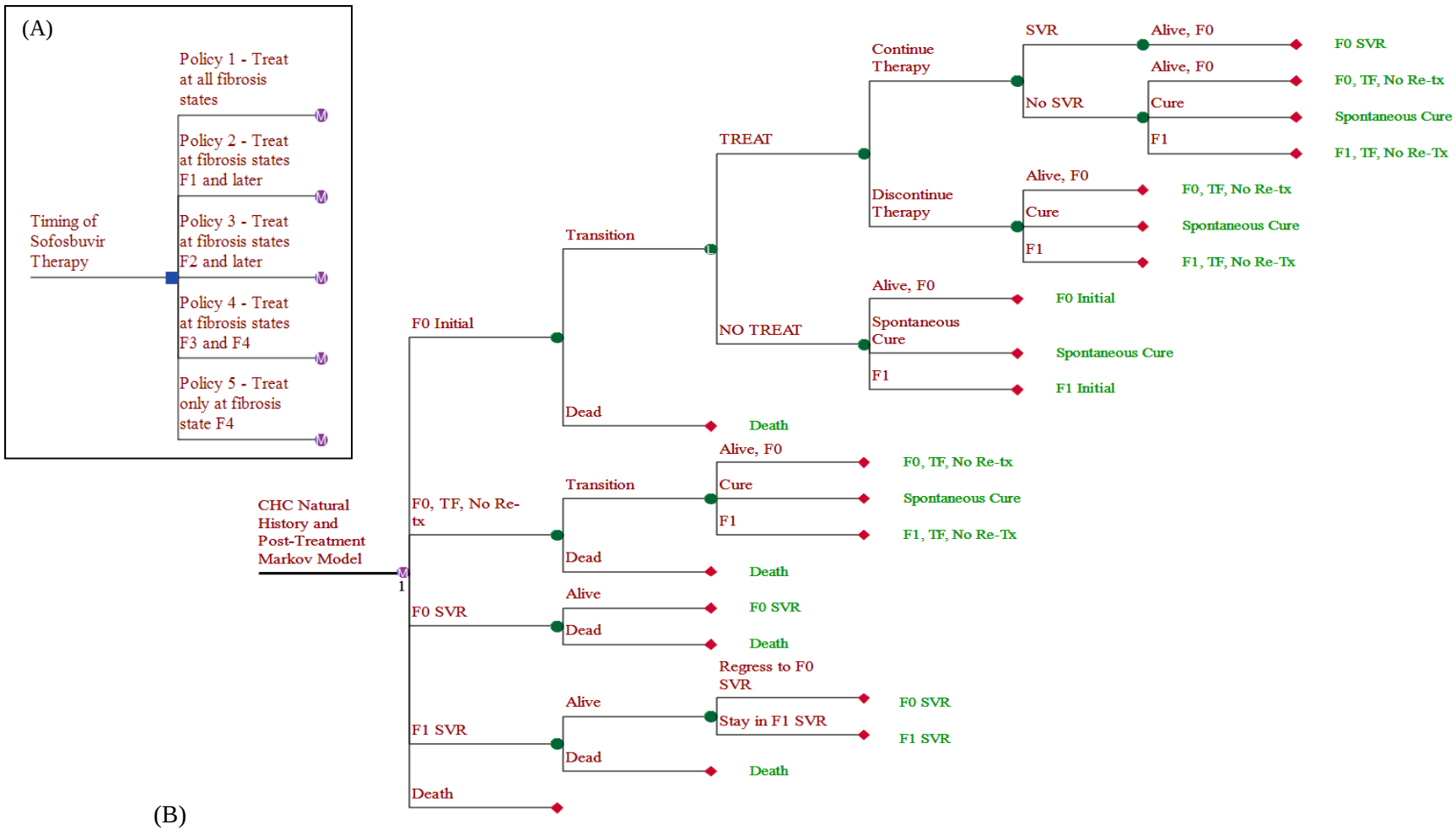
eFigure 1. Natural History Markov Model Describing HCV Progression Following No Treatment, Treatment Failure, or Discontinuation

eFigure 1 Legend: Patients enter the Markov model either when they receive no treatment, after unsuccessful therapy or treatment discontinuation, in fibrosis stages F0 through F4. The red arrows indicate disease state progression, black arrow indicates no progression and green arrow indicates spontaneous cure. Because it is not possible to screen out patients who will not progress, when they are treated at F0, the patients accrue all costs associated with therapy before being removed from subsequent progression to other disease states.



eFigure 2. Markov Model Showing Progression and Regression of CHC Following Successful Treatment (Post-SVR)

eFigure 2 Legend: Patients enter the Markov model after successful therapy in fibrosis stages 0 through 4. Blue arrows indicate proportional regression of fibrosis and stared numbers indicate the proportion of patients from the source state transitioning into a lower fibrosis state. The regression data covers a wide time range, between 1 and 10 years post regression. In this model the regression transition occurs immediately after successful treatment. Red arrows indicate annual probabilities of liver damage progression after successful treatment.



eFigure 3. Selected Nodes of the Tree Structure Associated With Each Policy

eFigure 3 Legend: As an example of the model structure, eFigure 3A depicts five policy decisions under consideration for treatment with sofosbuvir based therapy; and eFigure 3B shows the model tree structure at selected nodes for illustrative purposes. This generic structure shows only four of the 26 Markov states representing 16 health states. See eFigures 1 and 2 above; and eTable 4 for details of the Markov model. The Markov model structure is the similar for all policies. The policy analysis starts at the node marked with an 'M.' Then, within each policy, the fibrosis state in which the treatment is initiated is selected. The terminal nodes indicate the transition to other Markov states depending on the outcome of the cycle.

2. Description of methods for input costs

A. Cost of drugs: Microdex Red Book's Wholesale Acquisition Price. Societal.

B. Pre-SVR Medical care costs, among those identified in care: HMO unit cost data (McAdam-Marx, 2011), applied to utilization information extracted from electronic medical record. Societal.

C. Post-SVR Medical care costs: As above, but adjusted by midpoint of two pre- / post- cost ratios from two medical care data bases (Backx 2014; Manos, 2012). Societal.

D. HCV genotyping, therapy monitoring, including clinic visits, blood and hepatic tests, and HCV RNA quantification

   i. Medicare reimbursement schedule and Rein 2001. Societal.
   ii. Fibrosis staging cost data from Carlson 2009 which evaluated costs from health care payer perspective. In this context, health care payer perspective may be slightly less than full societal costs if there were deductibles or other out-of-pocket patient costs.

E. Side-effect management. These costs were estimated with trial-based AE rates and literature-based protocols, resource utilization and standard costs (Gao 2012). Societal.

3. Model calibration and validation

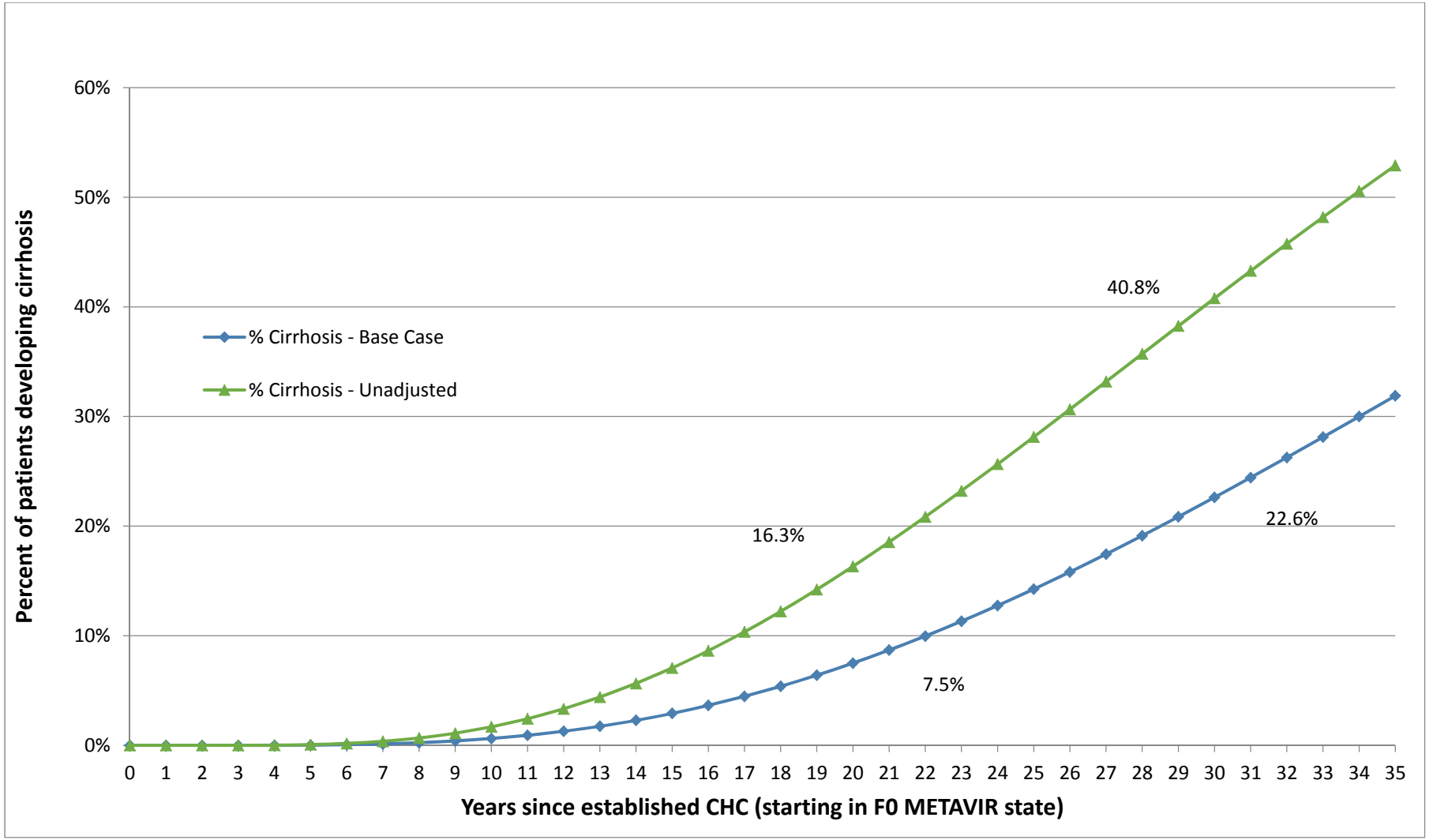
A. Model calibration

To calibrate and validate our model we compared the results of the natural history Markov with published studies. We ran multiple simulations to compare estimated progression to cirrhosis over 20 and 30 years. The estimates for progression to cirrhosis vary widely in literature, depending on patient population and study setting.[6-8] We used a well-recognized and widely-used meta-analysis of 33,000 HCV patients by Thein, et al and a published model by Hagan, et al to validate our model.[8,9]

First, we ran a simulation using the stage-specific METAVIR transition probabilities used by Thein, et al in their work to calibrate the model. In this simulation all patients started with established chronic hepatitis C in METAVIR stage F0 (no liver fibrosis) and followed patients over time to determine the cumulative proportion of patients who end up with cirrhosis at years 20 and 30. The results of this calibration are presented in eFigure 4 (green line). Thein and colleagues predicted a cumulative probability of cirrhosis to be 16% (95% CI, 14-19%) at year 20 and 41% (36-45%) at year 30.[8] Our model predicted cumulative probabilities to be 16.3% and 40.8% at years 20 and 30, respectively (eFigure 4). These values are very similar to those of Thein, et al and are within their 95% confidence intervals, indicating our model is well calibrated.

However, our base-case model uses a cohort aged 60 years, with HCV duration of greater than 20 years, and uses annual probabilities for progression through METAVIR stages that are lower than the typically used population probabilities. Our model assumes that the cohort was infected when patients were less than 30 years of age (in the 1970s and 80s). Evidence by Thein and colleagues suggests that these individuals are 2 to 3 times less likely to progress to cirrhosis than those infected at ages greater than 30 years.[8] Additionally, progression to cirrhosis is lower for those with longer (greater than 10 years) of infection – a characteristic of the modeled cohort.

Thus, we ran a simulation to determine the cumulative probability of developing cirrhosis in our base-case cohort and compare to the Thein et al predictions. The results are shown in eFigure 4. Our model predicted probability of developing cirrhosis to be 7.5% and 22.6% at years 20 and 30, respectively. The value of developing cirrhosis in this group at 20 years (7.5%) is consistent with the findings by Thein et al. However, the prediction of developing cirrhosis at 30 years in this population is slightly higher by 0.1% than the upper confidence limit of 22.5% (calculated by authors using estimates by Thein and colleagues). Overall, our model fits the predictions by Thein et al well.



eFigure 4. Model Calibration and Validation: Cumulative Probability of Developing Cirrhosis

eFigure 4 Legend: A simulation of a CHC cohort (age = 50 years) with METAVIR fibrosis score F0 (no liver fibrosis) was conducted to determine cumulative progression to cirrhosis. First, transition probabilities from a meta-analysis were used to compare cirrhosis probability with published findings (green line). Second, base-case transition probabilities were used to validate the cumulative probability of cirrhosis in the modeled population in which duration of CHC is greater than 20 years (blue line). The marked data points show the cumulative probability of cirrhosis at 20 and 30 years.

B. Model validation: Comparison of model analyses with published results:

Our model utilizes a regression of fibrosis post-SVR and allows for a full range of progression (from F0 to F4). Further, we allow for increased background mortality pre-SVR and post-SVR by a factor of 2.37 and 1.4, respectively, in F3 and F4 fibrosis stages only. To our knowledge no other currently published has modeled HCV in similar terms. Thus, a direct comparison of our findings to currently published models is not possible. However, we compared results of our model for treatment with sofosbuvir + simeprevir (Sim/Sof) and sofosbuvir + ribavirin (Sof/R) to a model published by Hagan, et al.[9] Hagan and colleagues allow for some regression and post-progression and they apply increased pre- and post-SVR mortality, similar to our model. However, the Hagan model does model regression to the extent our model does, nor does the model allow for post-SVR progression from F0-F4.[9] And the Hagan model applies increased mortality in all METAVIR stages (F0-F4), both pre- and post-SVR.[9] Additionally, the Hagan and colleagues modeled 90% retreatment with 24 weeks of sofosbuvir + ledipasvir (SOF/LDV), while our model does not allow for retreatment of patients who do not achieve SVR with the modeled treatment.[9] However, the Hagan model allows for a relative comparison of our model and thus is used for further validation of our model. The results of the comparison are available in **Error! Reference source not found.** below.

eTable 2: Model comparison using Sim/Sof and Sof/R treatment regimens

	Hagan, et al.		**This model**	
Regimen	Net Cost	QALYs	Net Cost	QALYs
Sim/Sof	$165,336	14.69	$179,526	14.83
Sof/R	$243,586	14.45	$188,337	13.85
Sim/Sof: sofosbuvir + simeprevir; Sof/R: sofosbuvir + ribavirin; QALYs: Quality adjusted life years				

Overall, our model produces results similar to those found by Hagan and colleagues. The differences in costs and QALYs can be explained by the model input differences in retreatment costs, health state related costs, efficacy rates and utilities. For example, Sof/R has a high treatment failure rate in the Hagan model (30%); retreatment of 90% of these patients would result in the substantially higher costs as seen here. And the retreatment of these patients would also add to the QALYs as 96% patients would achieve SVR after being treated with SOF/LDV.

In conclusion, the cross-validation of our model with published studies concludes that this model is appropriately calibrated to model chronic hepatitis C.

II. Input parameters for the hepatitis C model

eTable 3: Distribution of fibrosis stages in Chronic Hepatitis C population

CHC State	Definition	Siddiqui* [10]	Hagan† [4]	Coffin [11]	Thein [8]	This Model
F0	No fibrosis	0.18	0.14	0.20	0.17	0.17 (0.14-0.19)
F1	Portal fibrosis without septa	0.26	0.30	0.20	0.35	0.35 (0.26-0.39)
F2	Portal fibrosis with rare septa	0.18	0.19	0.20	0.22	0.22 (0.18-0.24)
F3	Numerous septa without	0.15	0.12	0.20	0.14	0.14 (0.12-0.15)
F4 (CC)	Compensated Cirrhosis	0.23‡	0.095	0.20	0.12	0.12 (0.11-0.13)

F0-F4 – METAVIR fibrosis score. CC – Compensated cirrhosis.
*Calculated from Siddiqui, et al.
†Study included decompensated cirrhosis distribution
‡Includes compensated cirrhosis and decompensated cirrhosis cases

eTable 4. Chronic Hepatitis C Natural History Disease Progression, Post-SVR Progression, and Regression and Mortality

Source State	Target State	Base case	Lower limit	Upper limit	Reference
Natural History					
F0	No progression (proportion)	0.24	0.10	0.40	[5]
	F1 (Age 20-29 years)	0.314	0.204	0.484	[8]
	F1 (Age 30-49 years)	0.131	0.115	0.148	[8]
	F1 (Age 50+ years)	0.077	0.067	0.088	[8]
	Spontaneous Resolution	0.002	0	0.005	[12]
F1	F2 (Age 20-29 years)	0.322	0.179	0.58	[8]
	F2 (Age 30-49 years)	0.08	0.069	0.093	[8]
	F2 (Age 50+ years)	0.074	0.064	0.086	[8]
F2	F3 (Age 20-29 years)	0.22	0.146	0.333	[8]
	F3 (Age 30-49 years)	0.133	0.119	0.15	[8]
	F3 (Age 50+ years)	0.089	0.077	0.103	[8]
F3	F4 (Age 20-29 years)	0.151	0.098	0.233	[8]
	F4 (Age 30-49 years)	0.134	0.117	0.15	[8]
	F4 (Age 50+ years)	0.088	0.075	0.104	[8]
	Decompensated Cirrhosis	0.012	0.01	0.014	[4]
	Hepatocellular Carcinoma[1]	0.00725	0	0.02669	[11]
F4 (Compensated Cirrhosis)	Decompensated Cirrhosis	0.039	0.03	0.048	[11]
	Hepatocellular Carcinoma	0.019	0.017	0.055	[11]
Decompensated Cirrhosis	Hepatocellular Carcinoma	0.014	0.011	0.017	[4]
	Liver Transplant	0.017	0.0169	0.045	[13]
	Death	0.129	0.1032	0.1548	[11]
Hepatocellular Carcinoma	Liver Transplant	0.017	0.0169	0.045	[13]
	Death	0.4270	0.3416	0.5124	[11]
Liver Transplant	Death (Year 1)	0.107	0.09	0.13	[13]
	Death (Year 2+)	0.0485	0.0385	0.0585	[13]
CHC Progression Post-SVR					
F0	F1	Reduced by 91.4% of pre-SVR probability as listed above, by age group.			Calculated*
F1	F2				Calculated*
F2	F3				Calculated*
F3	F4				Calculated*
	Decompensated Cirrhosis	0.001028	0.0005	0.0015	[11]
	Hepatocellular Carcinoma	0.004753	0.001	0.007	[11]
F4	Decompensated Cirrhosis	0.003342	0.002	0.005	[11]
	Hepatocellular Carcinoma	0.012449	0.006	0.019	[11]
Decompensated Cirrhosis	Hepatocellular Carcinoma	0.010	0.008	0.017	[4]
	Liver Transplant	0.012	0.007	0.016	[13]
	Death	0.09	0.07	0.15	[4]
Fibrosis Regression Post-SVR (Proportions)					
F1	F0	0.35	0.17	0.52	[14-17]
F2	F0	0.12	0.06	0.18	[14-17]
	F1	0.58	0.29	0.87	[14-17]

F3	F1	0.24	0.12	0.36	[14-17]
	F2	0.46	0.23	0.69	[14-17]
F4	F1	0.09	0.05	0.14	[14-21]
	F2	0.14	0.07	0.21	[14-21]
	F3	0.22	0.11	0.33	[15-18,20,22]
Background Mortality					
CHC all-cause mortality ratio	Compared to no CHC (general population)	2.37†	1.28	4.38	[23]
All-cause mortality ratio after SVR	Compared to no CHC (general population)	1.4†	1.0	2.5	[24]
Background mortality	Death	Age-specific mortality from US 2009 Life Tables			[25]

F0-F4 – METAVIR fibrosis score.

*Clinical evidence on annual probabilities for post-SVR progression in these states is limited; authors elected to take a conservative approach and model progression at a substantially reduced probability. The reduction in annual probability is calculated based on a 91.4% reduction in progression from F3 to DC after SVR compared to natural history.

†Increased by 2.37 or 1.4 for patients in F3, F4 fibrosis stages with CHC and after SVR, respectively (patients in F0-F2 stages experience the same baseline mortality as no-CHC population based on 2009 US life tables).

eTable 5: Weekly cost of drugs for the modeled therapies

Drug	Base Case	Lower limit*	Upper limit*	Source
Weekly drug costs (cost in 2015 US dollars)†				
PegINF 180mcg SQ injection QWeekly	789	395	1184	[26]
Ribavirin 1200mg daily	46	23	69	[26]
Simeprevir 150mg QD	5,530	2,765	8,295	[26]
Sofosbuvir 400mg QD	7,000	3,500	10,500	[26]
Ledipasvir 90mg + Sofosbuvir 400mg (QD, FDC)	7,875	3,938	11,813	[26]
Ombitasvir, Paritaprevir/Ritonavir 12.5/75/50mg 2 tablets, QD; Dasabuvir 250mg BID	6,943	3,472	10,415	[26]

SQ: Subcutaneous injection; QWeekly: Once a week; QD: Once daily; FDC: Fixed Dose Combination; BID: Twice daily

*The lower and upper bounds for SA are set at 50%-150% of base case.

†Wholesale Acquisition Cost (WAC) – from Red Book Online - USD February 2015. When multiple costs were available, the cheapest cost for a 7-day supply was used.

eTable 6: Chronic Hepatitis C healthcare costs by disease state

Health State (costs in 2014 US dollars)*	Base case	Lower limit‡	Upper limit‡	Reference
Annual cost of CHC-related healthcare by disease state				
F0 – No fibrosis†	810	405	3,240	[13,27,28]
F1 – Portal Fibrosis without septa†	810	405	3,240	[13,27,28]
F2 – Portal fibrosis with rare septa†	810	405	3,240	[13,27,28]
F3 – Numerous septa without	2,150	1,075	8,600	[13,27,28]
F4 – Compensated cirrhosis	2,575	1,287	10,298	[13,27,28]
Decompensated cirrhosis	30,494	28,619	32,370	[13,29]
Hepatocellular carcinoma	48,641	43,654	53,622	[13]
Liver transplant, year 1	193,101	178,071	208,126	[13]
Liver transplant, year 2+	42,056	34,364	49,747	[13]
Post-SVR costs for F0-F4	50% of no SVR			[27,28]

*All costs adjusted to December 2014 US dollars using the CPI Medical Component.

†F0 to F3 costs based on $900 weighted average. The cost gradient from F0 to F3 leading into F4 costs was established using fibrosis stage prevalence.

‡Range for deterministic and probabilistic analyses for F0-F4 health state costs is 50% to 300%, to account for any uncertainty in the base-case values.

eTable 7: Other healthcare related costs – follow up, testing and management of treatment

Test or Office Visit (costs in 2014 US dollars)*	Base case	Lower limit†	Upper limit†	Reference
Treatment related medical care costs (excluding drugs)‡				
Anti-HCV (antibody) test	26	13	39	[30]
HCV RNA quantification	79	39	118	[30]
Genotype assay	475	237	712	[30]
CBC w/Differential	14	7	22	[30]
Hepatic function panel	15	8	23	[30]
Office visit (outpatient)	97	49	146	[31]
Fibrosis assessment	262	131	393	[32]

*All costs adjusted to December 2014 US dollars using the CPI Medical Component.
†The lower and upper bounds for SA are set at 50%-150% of base case value.
‡Cost per unit. For intervals of when the tests and office visits take place (and the number of each unit modeled), see eTable 8.

eTable 8: Frequency, by week, of follow up/testing/management of each treatment modality

Test and Office Visit	8-week therapy	12-week therapies				24-week therapies			48-week therapy
	SOF/LDV*	Sof/PR	SOF/LDV	Sim/Sof	3D	Sof/R	3D	Sim/Sof	P/R
Anti-HCV (antibody) test	0 (#1)†, ‡	0 (#1)				0 (#1)			0 (#1)
Genotype assay	0 (#1)‡	0 (#1)				0 (#1)			0 (#1)
Fibrosis assessment	0 (#1)‡	0 (#1)				0 (#1)			0 (#1)
HCV RNA quantification	0, 4, 8, 12 (#4)‡	0, 4, 8, 12, 24 (#5)				0, 4, 8, 12, 24, 36 (#6)			0, 4, 12, 24, 60 (#6)
CBC w/Differential	0, 4, 8, 12 (#4)‡	0, 4, 8, 12, 24 (#5)				0, 4, 8, 12, 16, 24, 36 (#7)			0, 4, 8, 12, 16, 24, 48, 60 (#7)
Hepatic function panel	0, 4, 8, 12 (#4)‡	0, 4, 8, 12, 24 (#5)				0, 4, 8, 12, 16, 24, 36 (#7)			0, 4, 8, 12, 16, 24, 48, 60 (#7)
Office visit (outpatient)	0, 4, 8, 12 (#4)‡	0, 4, 8, 12, 24 (#5)				0, 4, 8, 12, 16, 24, 36 (#7)			0, 4, 8, 12, 16, 24, 48, 60 (#7)

P/R = Peg-interferon + Ribavirin; Sof/PR = Sofosbuvir + PegINF/R; Sof/R = Sofosbuvir + Ribavirin; SOF/LDV = Sofosbuvir + Ledipasvir; Sim/Sof = Sofosbuvir + Simeprevir; 3D = Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir ± Ribavirin;
– indicates the quantity of tests or office visits over the course of treatment.
*67% of treatment naïve, non-cirrhotic patients receive 8-weeks of therapy in base-case scenario, remaining receive 12-weeks of therapy.
†Week (i.e. 0, 2, 4, etc.) at which the test or office visit takes place.
‡Per AASLD guidelines and an additional test at 12-weeks after end-of-treatment.[33]

eTable 9: Total cost of treatment associated adverse events

Adverse events treatment costs (2014 USD)*				
Treatment Modality (Duration)	Base case†	Min‡	Max‡	Reference
P/R (48 weeks)	2,073	1,037	3,110	Calculated
Sof/PR (12 weeks)	1,719	860	2,579	Calculated
Sof/R (24 weeks)	967	484	1,451	Calculated
Sim/Sof (12 weeks)	764	382	1,146	Calculated
Sim/Sof (24 weeks)	1,135	567	1,702	Calculated
SOF/LDV (8 weeks)	346	173	519	Calculated
SOF/LDV (12 weeks)	456	228	683	Calculated
3D (12 weeks)	811	406	1,217	Calculated
3D (24 weeks)	1,048	524	1,572	Calculated

P/R = Peg-interferon + Ribavirin; Sof/PR = Sofosbuvir + PegINF/R; Sof/R = Sofosbuvir + Ribavirin; SOF/LDV = Sofosbuvir + Ledipasvir; Sim/Sof = Sofosbuvir + Simeprevir; 3D = Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir ± Ribavirin.

*All costs adjusted to December 2014 US dollars using the CPI Medical Component.

†Based on cost of serious adverse events of $2,706 and cost of common adverse events of $516. Costs are weighted by frequency of serious and common adverse events and summed to calculate the costs in the table.

‡The lower and upper bounds for SA are set at 50%-150% of base case value.

eTable 10: Health state utilities in Chronic Hepatitis C

Health State	Base case	Lower limit	Upper limit	Reference
Utilities for HCV states				
F0	0.98	0.92	1	[5,34]
F1	0.98	0.92	1	[5,34]
F2	0.92	0.72	1	[34]
F3	0.79	0.77	0.81	[35]
F4 (Compensated Cirrhosis)	0.76	0.70	0.79	[35]
Decompensated Cirrhosis	0.69	0.44	0.69	[35]
Hepatocellular Carcinoma	0.67	0.60	0.72	[35]
Liver Transplant, Year 1	0.5	0.40	0.69	[35]
Liver Transplant, Year 2+	0.77	0.57	0.77	[35]
Death	0	0	0	
Utilities after SVR per Markov cycle				
SVR F0	1	0.98	1	[5]
SVR F1	1	0.98	1	[5]
SVR F2	0.933	0.92	1	[5]
SVR F3	0.86	0.82	0.90	[4]
SVR Compensated Cirrhosis	0.83	0.79	0.87	[4]

eTable 11: Utility loss with Chronic Hepatitis C treatment

Treatment Modality (Duration)	Annualized utility loss*	Base case (during treatment)†	Lower limit‡	Upper limit‡	Reference
Utility penalties during treatment					
P/R (48 weeks)	-0.1931	-0.1782	-0.28965	0	Calculated§
Sof/PR (12 weeks)	-0.1485	-0.0343	-0.05145	0	Calculated§
Sof/R (24 weeks)	-0.0856	-0.0395	-0.05925	0	Calculated§
Sim/Sof (12 weeks)	-0.0687	-0.0159	-0.02385	0	Calculated§
Sim/Sof (24 weeks)	-0.0984	-0.0454	-0.0681	0	Calculated§
SOF/LDV (8 weeks)	-0.0319	-0.0049	-0.00735	0	Calculated§
SOF/LDV (12 weeks)	-0.0424	-0.0098	-0.0147	0	Calculated§
3D (12 weeks)	-0.0759	-0.0175	-0.02625	0	Calculated§
3D (24 weeks)	-0.0973	-0.0449	-0.06735	0	Calculated§

P/R = Peg-interferon + Ribavirin; Sof/PR = Sofosbuvir + PegINF/R; Sof/R = Sofosbuvir + Ribavirin; SOF/LDV = Sofosbuvir + Ledipasvir; Sim/Sof = Sofosbuvir + Simeprevir; 3D = Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir ± Ribavirin.

*Total calculated utility loss over a 52-week period based on common and serious adverse events observed in clinical trials.

†Adjusted for treatment duration; for example for Sof/PR = (0.1485/52)*12))=0.0343.

‡Lower Limit is 50% more than the base-case. Upper Limit is no utility loss. For P/R the Lower Limit as shown is 50% more than the annualized utility loss.

§The utility loss due to adverse events was weighted by the frequency of common and serious adverse events as observed in clinical trials.

eTable 12: SVR and treatment discontinuation rates of all modeled therapies, based on meta-analyses of clinical trials

Treatment	Subgroup	Treatment Duration	SVR (95% CI)*	D/C (95% CI)	Reference
Sof/PR	Treatment Naïve, no cirrhosis	12 weeks	0.925 (0.894-0.952)	0.095 (0.065-0.129)	[36-38]
	Treatment Naïve, + cirrhosis	12 weeks	0.818 (0.696-0.918)	0.105 (0.028-0.211)	
Sof/R	Treatment Naïve, no cirrhosis	24 weeks	0.699 (0.448-0.905)	0.079 (0.011-0.184)	[39,40]
	Treatment Naïve, + cirrhosis	24 weeks	0.714 (0.419-0.916)	0.000 (0.000-0.459)	
Sim/Sof	Treatment Naïve, no cirrhosis	12 weeks	1.00 (0.398-1.00)	0.000 (0.000-0.602)	[41,42]
	Treatment Naïve, + cirrhosis	24 weeks	1.00 (0.541-1.00)	0.167 (0.004-0.641)	
SOF/LDV[†]	Treatment Naïve, no cirrhosis	8 weeks	0.948 (0.913-0.976)	0.002 (0.000-0.018)	[43-47]
	Treatment Naïve, no cirrhosis	12 weeks	0.985 (0.945-1.00)	0.014 (0.000-0.049)	
	Treatment Naïve, + cirrhosis	12 weeks	0.984 (0.879-1.00)	0.000 (0.000-0.075)	
3D±R	GT1a[‡]				[48-51]
	Treatment Naïve, no cirrhosis (+R)	12 weeks	0.962 (0.941-0.979)	0.008 (0.000-0.033)	
	Treatment Naïve, cirrhosis (+R)	24 weeks	0.923 (0.815-0.979)	0.058 (0.012-0.159)	
	GT1b[‡]				
	Treatment Naïve, no cirrhosis	12 weeks	0.996 (0.980-1.00)	0.021 (0.000-0.134)	
	Treatment Naïve, cirrhosis (+R)	12 weeks	1.00 (0.877-1.00)	0.000 (0.000-0.123)	
P/R[4]	EVR12[§]	--	0.799 (0.40-1.00)[‖, ¶]	--	[52-54]
	SVR followed by EVR12	48 weeks	0.683 (0.34-0.85)[¶]	0.242 (0.120-0.360)	

P/R = Peg-interferon + Ribavirin; Sof/PR = Sofosbuvir + PegINF/R; Sof/R = Sofosbuvir + Ribavirin; SOF/LDV = Sofosbuvir + Ledipasvir; Sim/Sof = Sofosbuvir + Simeprevir; 3D = Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir ± Ribavirin.

D/C = Discontinuation rate.

*SVR rates in the model are operationalized by adjusting for discontinuation rates using the following equation – SVR' = (SVR)/(1-D/C).

[†]For base-case, 67% of non-cirrhotic patients were allocated to receive SOF/LDV 8/12, while the remaining received 12 weeks of SOF/LDV therapy. This value was varied in one-way and probabilistic sensitivity analyses using a range of (30% to 90%).

[‡]GT1a / GT1b distribution used in this model in based on data from NHANESIII – GT1a – 77%, GT1b – 33%. The values were varied widely in one-way and probabilistic sensitivity analyses using GT1a range of (38.5% to 100%).

[§]Response guided therapy is modeled for P/R. EVR = Extended Virologic Response at week 12 of therapy for peg-interferon + ribavirin response guided therapy.

[‖]Probability of achieving EVR12.

[¶]Lower and upper bounds are 50% to 125% of base-case, selected by authors.

III. Additional results – Base-case results, health outcomes and budget impact

1. Base-case results for all treatment options and treatment policies

eTable 13: Base case results – treatment by fibrosis stage and treat all vs. Treat at F3/F4 strategies, for all treatment options

Strategy	Total Treatment Costs ($)	Incr. Costs ($)	QALYs	Incr. QALYs	ICER ($/QALY)*	Probability (%) of Cost-effectiveness†		
						WTP‡: $50,000	WTP‡: $100,000	WTP‡: $150,000
Base-case results for treat all vs. Treat at F3/F4								
Treatment Option: P/R								
Treat at F3/F4§	48,054	-	12.97	0.00	-	31	18	13
Treat All‖	61,499	13,445	13.34	0.38	35,691	69	82	87
Treatment Option: Sof/PR								
Treat at F3/F4	70,554	-	13.89	0.00	-	25	10	5
Treat All	107,725	37,171	14.57	0.68	54,859	75	90	95
Treatment Option: Sof/R								
Treat at F3/F4	116,687	-	13.32	0.00	-	58	36	23
Treat All	188,337	71,650	13.85	0.53	134,568	42	64	77
Treatment Option: Sim/Sof								
Treat at F3/F4	115,052	-	14.05	0.00	0	62	41	27
Treat All	179,526	64,475	14.83	0.78	82,644	38	59	73
Treatment Option: SOF/LDV (8/12)¶								
Treat at F3/F4	60,906	-	14.09	0.00	0	16	5	3
Treat All	89,804	28,899	14.82	0.73	39,475	84	95	97
Treatment Option: SOF/LDV (12)								
Treat at F3/F4	69,382	-	14.14	-	-	23	8	5
Treat All	107,528	38,146	14.89	0.75	50,927	77	92	95
Treatment Option: 3D±R								
Treat at F3/F4	71,109	-	14.05	0.00	0	19	6	4
Treat All	105,289	34,180	14.80	0.75	45,409	81	94	96

eTable 13: Base case results – treatment by fibrosis stage and treat all vs. Treat at F3/F4 strategies, for all treatment options (continued)

Strategy	Total Treatment Costs ($)	Incr. Costs ($)	QALYs	Incr. QALYs	ICER ($/QALY)*	Probability (%) of Cost-effectiveness†		
						WTP‡: $50,000	WTP‡: $100,000	WTP‡: $150,000
Base-case results by fibrosis stage								
Treatment Option: P/R								
No Treatment	46,107	-	11.82	0.00	-	1	0	0
Treat at F4	46,139	31	12.33	0.51	61	1	0	0
Treat at F3	48,054	1,916	12.97	0.63	3,020	13	8	7
Treat at F2	53,229	5,174	13.29	0.32	16,183	44	37	30
Treat at F1	58,672	5,443	13.34	0.05	100,606	27	31	32
Treat All	61,499	2,827	13.34	0.00	991,163	14	24	31
Treatment Option: Sof/PR								
No Treatment	46,107	-	11.82	0.00	-	0	0	0
Treat at F4	59,292	13,185	12.66	0.83	15,827	0	0	0
Treat at F3	70,554	24,447	13.89	2.07	11,837	10	5	3
Treat at F2	85,002	14,448	14.41	0.52	27,890	43	26	16
Treat at F1	99,859	14,857	14.54	0.13	113,575	28	32	29
Treat All	107,725	7,866	14.57	0.03	273,668	18	37	52
Treatment Option: Sof/R								
No Treatment	46,107	-	11.82	0.00	-	25	4	1
Treat at F4	88,831	42,723	12.31	0.49	87,700	3	1	0
Treat at F3	116,687	70,580	13.32	1.49	47,244	14	12	9
Treat at F2	145,731	29,044	13.73	0.41	70,578	33	45	40
Treat at F1	173,737	28,006	13.83	0.10	279,823	21	27	30
Treat All	188,337	14,600	13.85	0.02	700,350	3	11	19
Treatment Option: Sim/Sof								
No Treatment	46,107	-	11.82	0.00	-	39	9	2
Treat at F3	115,052	68,944	14.05	2.23	30,902	1	2	2
Treat at F4	115,254	203	12.67	-1.39	Dominated	10	13	10
Treat at F2	140,857	25,805	14.65	0.60	43,273	28	41	40
Treat at F1	166,252	25,395	14.80	0.15	168,963	20	26	28
Treat All	179,526	13,275	14.83	0.03	396,035	2	9	16

eTable 13: Base case results – treatment by fibrosis stage and treat all vs. Treat at F3/F4 strategies, for all treatment options (continued)

Strategy	Total Treatment Costs ($)	Incr. Costs ($)	QALYs	Incr. QALYs	ICER ($/QALY)*	Probability (%) of Cost-effectiveness[†]		
						WTP[‡]: $50,000	WTP[‡]: $100,000	WTP[‡]: $150,000
Treatment Option: SOF/LDV (8/12)[¶]								
No Treatment	46,107	-	11.82	0.00	-	0	0	0
Treat at F4	57,616	11,509	12.85	1.02	11,252	0	0	0
Treat at F3	60,906	14,798	14.09	2.27	6,522	7	3	2
Treat at F2	71,913	11,007	14.65	0.55	19,833	34	17	10
Treat at F1	83,594	11,682	14.79	0.14	81,165	30	29	25
Treat All	89,804	6,210	14.82	0.03	187,065	30	51	64
Treatment Option: SOF/LDV (12)								
No Treatment	46,107	-	11.82	-	-	0	0	0
Treat at F4	57,616	11,509	12.85	1.02	11,252	0	0	0
Treat at F3	69,382	23,275	14.14	2.31	10,061	9	5	3
Treat at F2	84,160	14,778	14.70	0.57	26,005	40	23	14
Treat at F1	99,435	15,275	14.85	0.15	103,915	29	30	27
Treat All	107,528	8,093	14.89	0.03	239,813	22	42	56
Treatment Option: 3D±R								
No Treatment	46,107	-	11.82	0.00	-	0	0	0
Treat at F3	71,109	25,002	14.05	2.22	11,248	0	0	0
Treat at F4	73,338	2,228	12.78	-1.26	Dominated	8	4	3
Treat at F2	84,401	13,292	14.62	0.58	23,088	39	19	11
Treat at F1	98,091	13,690	14.77	0.14	94,533	31	32	28
Treat All	105,289	7,198	14.80	0.03	223,653	22	45	59

$ – United States Dollars; QALYs – Quality adjusted life years; ICER – Incremental Cost-Effectiveness Ratio; Results of base case analysis: arranged by increasing costs and QALYs.

*ICERs generated by comparing each policy to the one above (next least expensive).

[†]Probabilistic sensitivity analyses results (Monte Carlo simulations) – generated by varying all input variables simultaneously with 10,000 iterations of the model.

[‡]Willingness-to-pay threshold ($/QALY).

[§]Early Treatment: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4).

[||]Late Treatment: Wait and treat only when patients reach stages F3 and F4.

[¶]Stages F0-F3 – treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks.

2. Long-term health outcomes, for treatment with all options

eTable 14: Long-term health outcomes with treatment at an earlier fibrosis stage (or treat all) vs. treating at a later fibrosis stage (or treating at F3/F4) – number of advanced liver disease cases per 100,000 treated patients

Treatment Policy	Not Treated	P/R		Sof/PR		Sof/R		Sim/Sof		SOF/LDV (8/12)*		SOF/LDV (12)		3D	
	# Cases	# Cases	% Red.†	# Cases	% Red.	# Cases	% Red.	# Cases	% Red.	# Cases	% Red.	# Cases	% Red.	# Cases	% Red.
Treating all vs. treating at F3/F4															
Decompensated Cirrhosis															
Treat All‡	14,091	6,722	3	2,345	6	5,708	1	1,321	13	1,119	17	886	18	1,186	11
Treat at F3/F4§		6,915	Ref.	2,494	Ref.	5,775	Ref.	1,517	Ref.	1,351	Ref.	1,083	Ref.	1,334	Ref.
Hepatocellular Carcinoma															
Treat All	8,337	4,890	10	3,208	22	4,551	14	2,641	27	2,698	27	2,657	27	2,701	27
Treat at F3/F4		5,434	Ref.	4,122	Ref.	5,272	Ref.	3,608	Ref.	3,713	Ref.	3,640	Ref.	3,677	Ref.
Liver Transplants															
Treat All	1,347	699	8	296	15	615	7	177	23	184	26	167	24	185	18
Treat at F3/F4		757	Ref.	349	Ref.	660	Ref.	229	Ref.	247	Ref.	220	Ref.	225	Ref.
Death from Liver Complications‖															
Treat All	21,111	10,990	6	5,318	16	9,722	7	3,823	23	3,700	25	3,442	25	3,751	23
Treat at F3/F4		11,675	Ref.	6,334	Ref.	10,469	Ref.	4,957	Ref.	4,927	Ref.	4,595	Ref.	4,859	Ref.
Treatment by fibrosis stage															
Treat at F0	14,091	6688	0	2,352	0	5,692	0	1,270	0	1,100	0	889	0	1,182	0
Treat at F1		6704	1	2,358	--	5,708	0	1,271	1	1,103	4	890	1	1,180	0
Treat at F2		6750	2	2,339	7	5,706	3	1,280	14	1,150	13	897	18	1,178	16
Treat at F3		6858	23	2,514	63	5,859	39	1,483	76	1,327	73	1,092	77	1,400	73
Treat at F4		8911	Ref.	6,800	Ref.	9,584	Ref.	6,240	Ref.	4,915	Ref.	4,779	Ref.	5,277	Ref.
Hepatocellular Carcinoma															
Treat at F0	8,337	5036	0	3,246	0	4,476	0	2,641	0	2,748	0	2,580	0	2,699	0
Treat at F1		5032	1	3,248	1	4,472	1	2,643	2	2,748	3	2,585	2	2,698	2
Treat at F2		5068	9	3,280	22	4,501	12	2,687	26	2,834	23	2,638	27	2,746	25
Treat at F3		5553	22	4,203	43	5,142	34	3,612	48	3,678	48	3,596	48	3,676	47
Treat at F4		7155	Ref.	7,362	Ref.	7,755	Ref.	6,983	Ref.	7,065	Ref.	6,885	Ref.	6,876	Ref.

Liver Transplants															
Treat at F0	1,347	633	0	322	1	562	--	177	0	182	2	182	3	192	0
Treat at F1		636	5	324	2	557	4	177	1	186	4	187	--	192	--
Treat at F2		666	0	332	6	579	0	179	23	194	13	185	19	186	25
Treat at F3		665	24	355	58	578	43	232	64	223	63	227	61	249	56
Treat at F4		872	Ref.	851	Ref.	1,021	Ref.	636	Ref.	600	Ref.	586	Ref.	572	Ref.
Death from Liver Complications[‖]															
Treat at F0	21,111	11118	0	5,380	0	9,608	0	3,810	0	3,733	0	3,357	0	3,745	0
Treat at F1		11133	1	5,389	0	9,619	0	3,813	1	3,736	3	3,362	2	3,745	1
Treat at F2		11207	5	5,399	17	9,643	7	3,867	22	3,857	21	3,423	25	3,780	23
Treat at F3		11756	23	6,466	52	10,410	36	4,973	61	4,865	58	4,542	59	4,888	58
Treat at F4		15,241	Ref.	13,477	Ref.	16,388	Ref.	12,605	Ref.	11,451	Ref.	11,159	Ref.	11,595	Ref.

Treatment options: peg-interferon + ribavirin (P/R), sofosbuvir + peg-interferon/ribavirin (Sof/PR), sofosbuvir + ribavirin (Sof/R), sofosbuvir + ledipasvir (SOF/LDV), sofosbuvir + simeprevir (Sim/Sof) and ombitasvir, paritaprevir, ritonavir and dasabuvir ± ribavirin (3D).

*Stages F0-F3 – treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks

[†]Percent decrease in event outcome with treatment at an earlier fibrosis stage (or treat all) compared to treating at a later fibrosis stage (or treating at F3/F4). Percentages rounded to the nearest whole number.

[‡]Treat all: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4)

[§]Treat at F3/F4: Wait and treat only when patients reach stages F3 and F4

[‖]Liver complications = Decompensated Cirrhosis; Hepatocellular Carcinoma; and Liver Transplant

3. Budget impact analysis

eTable 15: Budget Impact, in total drug and health care costs, of therapies - treating all vs. treating at F3/F4

Strategy	Drug Costs ($)	Health Care Costs ($)	Total Treatment Costs ($)	25% treated*	50% treated*	75% treated*	100% treated*
Treatment Option: P/R							
Treat at F3/F4[†]	18,099	29,955	48,054	6,210,285,500	12,420,570,999	18,630,856,499	24,841,141,999
Treat All[‡]	34,365	27,134	61,499	11,791,485,041	23,582,970,083	35,374,455,124	47,165,940,165
Treatment Option: Sof/PR							
Treat at F3/F4	51,068	19,486	70,554	17,522,732,707	35,045,465,415	52,568,198,122	70,090,930,829
Treat All	92,797	14,928	107,725	31,840,920,467	63,681,840,933	95,522,761,400	127,363,681,867
Treatment Option: Sof/R							
Treat at F3/F4	90,048	26,639	116,687	30,897,749,782	61,795,499,564	92,693,249,346	123,590,999,128
Treat All	165,251	23,086	188,337	56,701,756,030	113,403,512,060	170,105,268,090	226,807,024,120
Treatment Option: Sim/Sof							
Treat at F3/F4	97,474	17,578	115,052	33,445,755,730	66,891,511,461	100,337,267,191	133,783,022,922
Treat All	167,031	12,495	179,526	57,312,508,010	114,625,016,021	171,937,524,031	229,250,032,041
Treatment Option: SOF/LDV (8/12)							
Treat at F3/F4	43,923	16,983	60,906	15,071,120,379	30,142,240,759	45,213,361,138	60,284,481,518
Treat All	77,644	12,160	89,804	26,641,591,066	53,283,182,131	79,924,773,197	106,566,364,262
Treatment Option: SOF/LDV (12)							
Treat at F3/F4	52,887	16,495	69,382	18,146,877,158	36,293,754,316	54,440,631,474	72,587,508,633
Treat All	95,989	11,539	107,528	32,936,242,017	65,872,484,034	98,808,726,052	131,744,968,069
Treatment Option: 3D±R							
Treat at F3/F4 Treatment	46,236	24,873	71,109	15,864,727,298	31,729,454,596	47,594,181,895	63,458,909,193
Treat All Treatment	85,326	19,963	105,289	29,277,413,924	58,554,827,848	87,832,241,772	117,109,655,696

Treatment options: peg-interferon + ribavirin (P/R), sofosbuvir + peg-interferon/ribavirin (Sof/PR), sofosbuvir + ribavirin (Sof/R), sofosbuvir + ledipasvir (SOF/LDV), sofosbuvir + simeprevir (Sim/Sof) and ombitasvir, paritaprevir, ritonavir and dasabuvir ± ribavirin (3D).
$ – United States Dollars
*Percent of the total 1.37 million genotype 1, treatment naïve patients treated with a given therapy
[†]Treat at F3/F4: Wait and treat only when patients reach stages F3 and F4
[‡]Treat All: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4)

IV. Sensitivity analyses

1. Scenarios analysis on Cost of Sofosbuvir/Ledipasvir

eTable 16: Sensitivity analyses results – 46% reduction in cost of Sofosbuvir/Ledipasvir

Strategy	Total Treatment Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICER ($/QALY)*
(A) Treat all vs. treat at F3/F4					
Treatment Option: SOF/LDV (8/12)[§]					
Treat at F3/F4[†]	41,266	-	14.09	-	-
Treat All[‡]	55,092	13,826	14.82	0.73	18,886
(B) By fibrosis stage					
Treatment Option: SOF/LDV (8/12)[§]					
Treat at F3	41,266	-	14.09	-	-
Treat at F4	44,029	2,763	12.85	(1.25)	Dominated
Treat at F2	46,091	4,825	14.65	0.55	8,694
No Treatment	46,107	16	11.82	(2.82)	(6)
Treat at F1	51,937	5,846	14.79	0.14	40,615
Treat All	55,092	3,156	14.82	0.03	95,052

$ – United States Dollars; QALYs – Quality adjusted life years; ICER – Incremental Cost-Effectiveness Ratio; Results of base case analysis: arranged by increasing costs and QALYs.
*ICERs generated by comparing each policy to the one above (next least expensive).
[†]Treat at F3/F4: Wait and treat only when patients reach stages F3 and F4.
[‡]Treat All: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4).
[§]Stages F0-F3 – Sofosbuvir/Ledipasvir treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks.

2. Scenarios analysis on Age

The base-case age used in our model is 60 years of age, determined based on the average of age of the patient presenting for care (a function of duration of infection). We also simulated a cohort of 50 years of age to determine the impact of treatment on cost, effectiveness and cost-effectiveness (ICER). As expected, compared to base-case results (eTable 13), treating at age 50 (10 years younger than base-case cohort), results in slightly increased total costs (likely due to increase health care costs), higher QALY gain (with an increase in incremental QALYs), resulting in overall more attractive ICERs.

eTable 17: Scenario analysis - Age 50 - by treat all vs Treat at F3/F4

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICER ($/QALY)*
PR					
Treat at F3/F4[†]	59,065	-	15.74	-	-
Treat All[‡]	70,051	10,986	16.24	0.50	21,856
SofPR					
Treat at F3/F4	79,876	-	16.96	-	-
Treat All	111,665	31,789	17.84	0.89	35,838
Sof+R					
Treat at F3/F4	132,200	-	16.19	-	-
Treat All	195,283	63,083	16.88	0.69	91,189
SOF/LDV (8/12 weeks)[§]					
Treat at F3/F4	68,722	-	17.23	-	-
Treat All	92,967	24,245	18.18	0.95	25,443
SOF/LDV (12 weeks)					
Treat at F3/F4	77,949	-	17.29	-	-
Treat All	110,471	32,522	18.27	0.98	33,337
Sim/Sof					
Treat at F3/F4	126,876	-	17.21	-	-
Treat All	182,946	56,070	18.21	1.01	55,723
3D					
Treat at F3/F4	79,775	-	17.19	-	-
Treat All	108,681	28,906	18.16	0.97	29,763

$ – United States Dollars; QALYs – Quality adjusted life years; ICER – Incremental Cost-Effectiveness Ratio; Treatment options: peg-interferon + ribavirin (P/R), sofosbuvir + peg-interferon/ribavirin (Sof/PR), sofosbuvir + ribavirin (Sof/R), sofosbuvir + ledipasvir (SOF/LDV), sofosbuvir + simeprevir (Sim/Sof) and ombitasvir, paritaprevir, ritonavir and dasabuvir ± ribavirin (3D).

*ICERs generated by comparing each policy to the one above (next least expensive).

[†]Treat at F3/F4: Wait and treat only when patients reach stages F3 and F4.

[‡]Treat All: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4).

[§]Stages F0-F3 – Sofosbuvir/Ledipasvir treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks.

eTable 18: Scenario analysis - Age 50 - by fibrosis stage

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICER ($/QALY)*
PR					
Treat at F3	59,065	-	15.74	-	-
Treat at F4	59,401	337	14.91	(0.83)	Dominated
No Treatment	61,174	2,110	14.11	(1.63)	Dominated
Treat at F2	62,888	3,823	16.15	0.41	9,220
Treat at F1	67,483	4,595	16.24	0.08	56,794
Treat All	70,051	2,568	16.24	0.01	363,072
SofPR					
No Treatment	61,174	-	14.11	-	-
Treat at F4	72,966	11,792	15.36	1.26	9,396
Treat at F3	79,876	18,702	16.96	2.85	6,558
Treat at F2	91,679	11,803	17.64	0.68	17,316
Treat at F1	104,443	12,764	17.81	0.17	74,798
Treat All	111,665	7,222	17.84	0.03	207,691
Sof+R					
No Treatment	61,174	-	14.11	-	-
Treat at F4	109,267	48,093	14.85	0.74	64,892
Treat at F3	132,200	71,026	16.19	2.08	34,108
Treat at F2	157,305	25,105	16.72	0.53	46,927
Treat at F1	181,745	24,440	16.85	0.13	186,238
Treat All	195,283	13,538	16.88	0.03	529,396
SOF/LDV (8/12 weeks)†					
No Treatment	61,174	-	14.11	-	-
Treat at F3	68,722	7,548	17.23	3.13	2,415
Treat at F4	70,445	1,722	15.64	(1.59)	Dominated
Treat at F2	77,355	8,632	17.96	0.73	11,859
Treat at F1	87,298	9,944	18.14	0.19	53,584
Treat All	92,967	5,669	18.18	0.04	143,833
SOF/LDV (12 weeks)					
No Treatment	61,174	-	14.11	-	-
Treat at F4	70,445	9,270	15.64	1.54	6,025
Treat at F3	77,949	16,775	17.29	3.19	5,262
Treat at F2	89,944	11,995	18.04	0.75	16,087
Treat at F1	103,047	13,104	18.23	0.19	69,057
Treat All	110,471	7,423	18.27	0.04	184,947
Sim/Sof					
No Treatment	61,174	-	14.11	-	-
Treat at F3	126,876	65,702	17.21	3.10	21,175
Treat at F4	139,289	12,413	15.39	(1.82)	Dominated
Treat at F2	148,661	21,785	17.98	0.77	Dominated
Treat at F1	170,685	22,024	18.17	0.19	113,518
Treat All	182,946	12,260	18.21	0.04	306,253
3D					
No Treatment	61,174	-	14.11	-	-
Treat at F3	79,775	18,600	17.19	3.09	6,027
Treat at F4	89,527	9,752	15.56	(1.63)	Dominated
Treat at F2	90,377	10,602	17.94	0.75	14,219
Treat at F1	102,089	11,713	18.12	0.19	62,602
Treat All	108,681	6,591	18.16	0.04	171,250

$ – United States Dollars; QALYs – Quality adjusted life years; ICER – Incremental Cost-Effectiveness Ratio; Treatment options: peg-interferon + ribavirin (P/R), sofosbuvir + peg-interferon/ribavirin (Sof/PR), sofosbuvir + ribavirin (Sof/R), sofosbuvir + ledipasvir (SOF/LDV), sofosbuvir + simeprevir (Sim/Sof) and ombitasvir, paritaprevir, ritonavir and dasabuvir ± ribavirin (3D).
*ICERs generated by comparing each policy to the one above (next least expensive).
[†]Stages F0-F3 – Sofosbuvir/Ledipasvir treatment duration for 67% of patients is 8 weeks, duration for 33% is 12 weeks; F4 – treatment duration is 12 weeks.

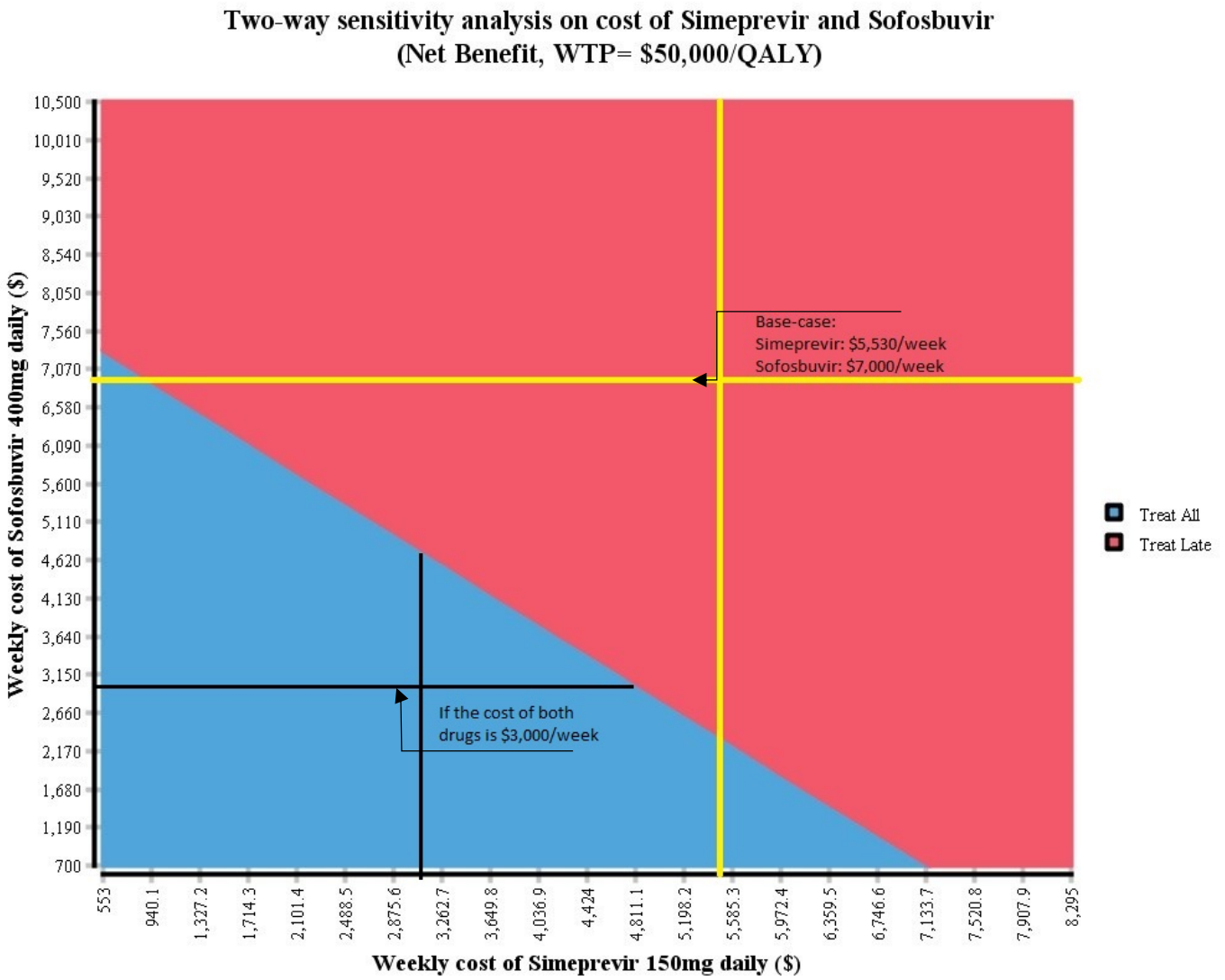
3. Sensitivity analyses on cost of Simeprevir and Sofosbuvir

Although an effective therapy, the combination of Sim/Sof (drugs from two different manufacturers), costs $12,500/week, more than both SOF/LDV ($7,875/week) and 3D ($6943/week). Therefore, we conducted two additional analysis on this treatment option: 1) sensitivity analysis with a 46% price reduction in the weekly cost of Sim/Sof (similar to the price reduction announced Gilead, manufacturer of SOF/LDV); and 2) a two-way sensitivity analysis on cost of sofosbuvir and simeprevir to determine what the costs of the two drugs would need to be in order for treating early with Sim/Sof to be considered highly cost-effective (at a WTP threshold of $50,000/QALY). As seen in eTable 19: , the results of 46% price reduction and compared to the base case analysis (eTable 13), the ICERs are more attractive. For example, the base-case ICER for treating all vs treating at F3/F4 is $82,644/QALY compared to $42,348/QALY in this analysis. In the two-way sensitivity analysis (eFigure 5) the possible range of costs for simeprevir and sofosbuvir for which treating early is cost-effect at a WTP of $50,000 is observed. For example, the costs of sofosbuvir and simeprevir would need to decrease to about $4,500/week and $3,200/week, respectively, for treating early to become cost-effective. The base-case (WAC) costs of sofosbuvir and simeprevir are $7,000/week and $5,530/week, respectively.

eTable 19: Sensitivity analyses results – 46% reduction in cost of Sim/Sof

Strategy	Total Treatment Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICER ($/QALY)*
Treat all vs. Treat at F3/F4					
Treatment Option: Sim/Sof					
Treat at F3/F4[†]	70,903	-	14.05	-	-
Treat All[‡]	103,940	33,038	14.83	0.78	42,348
By fibrosis stage					
Treatment Option: Sim/Sof					
No Treatment	46,107	-	11.82	-	-
Treat at F3	70,903	24,795	14.05	2.23	11,114
Treat at F4	76,629	5,727	12.67	(1.39)	Dominated
Treat at F2	83,691	12,789	14.65	0.60	21,446
Treat at F1	96,959	13,267	14.80	0.15	88,273
Treat All	103,940	6,982	14.83	0.03	208,293

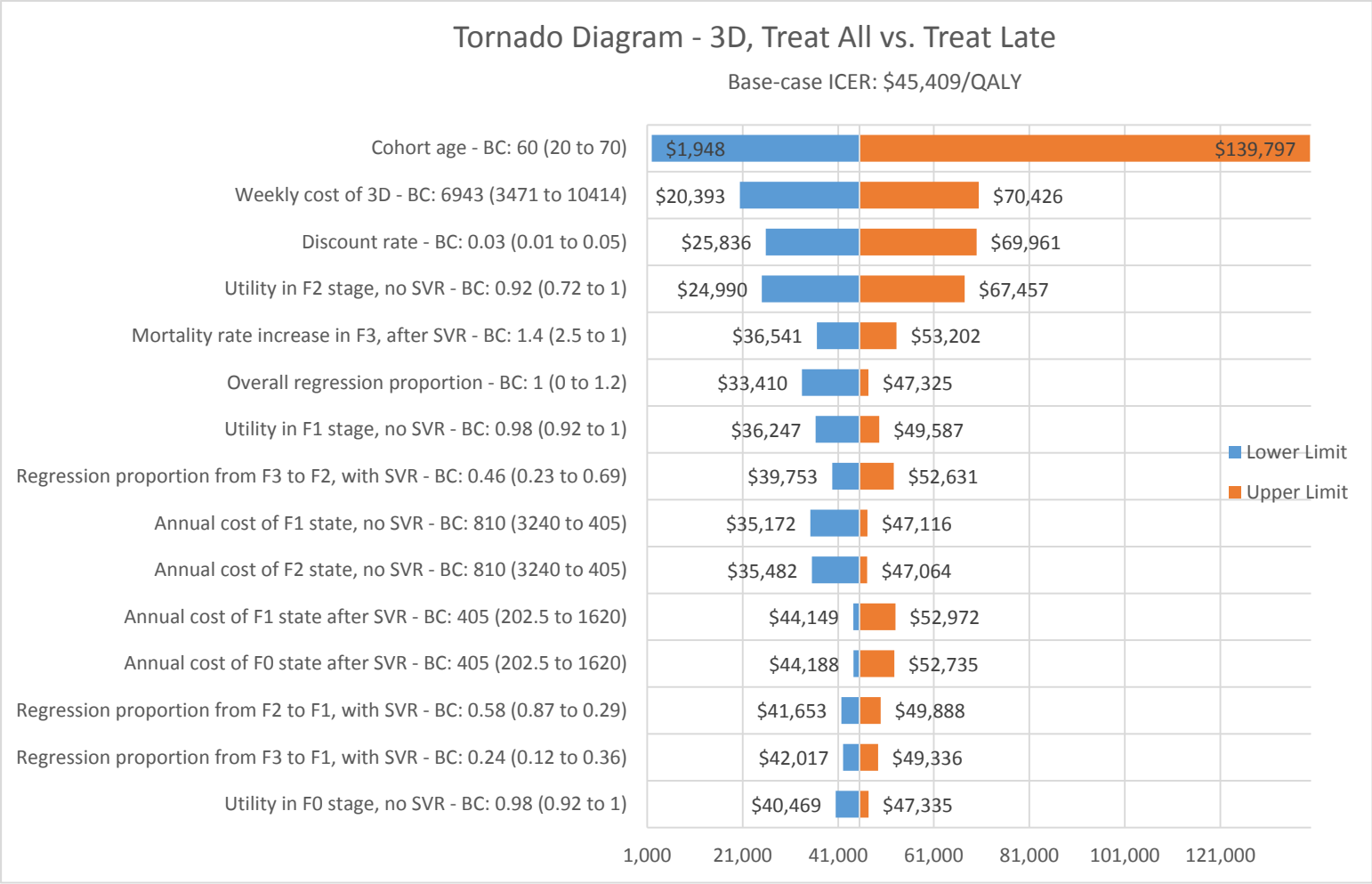
$ – United States Dollars; QALYs – Quality adjusted life years; ICER – Incremental Cost-Effectiveness Ratio; Results of base case analysis: arranged by increasing costs and QALYs.
*ICERs generated by comparing each policy to the one above (next least expensive).
[†]Treat at F3/F4: Wait and treat only when patients reach stages F3 and F4.
[‡]Treat All: Treat all patients as soon as they are identified with HCV in any stage (F0, F2, F2, F3 and F4).



eFigure 5: Two-way sensitivity analysis on cost of sofosbuvir and simeprevir

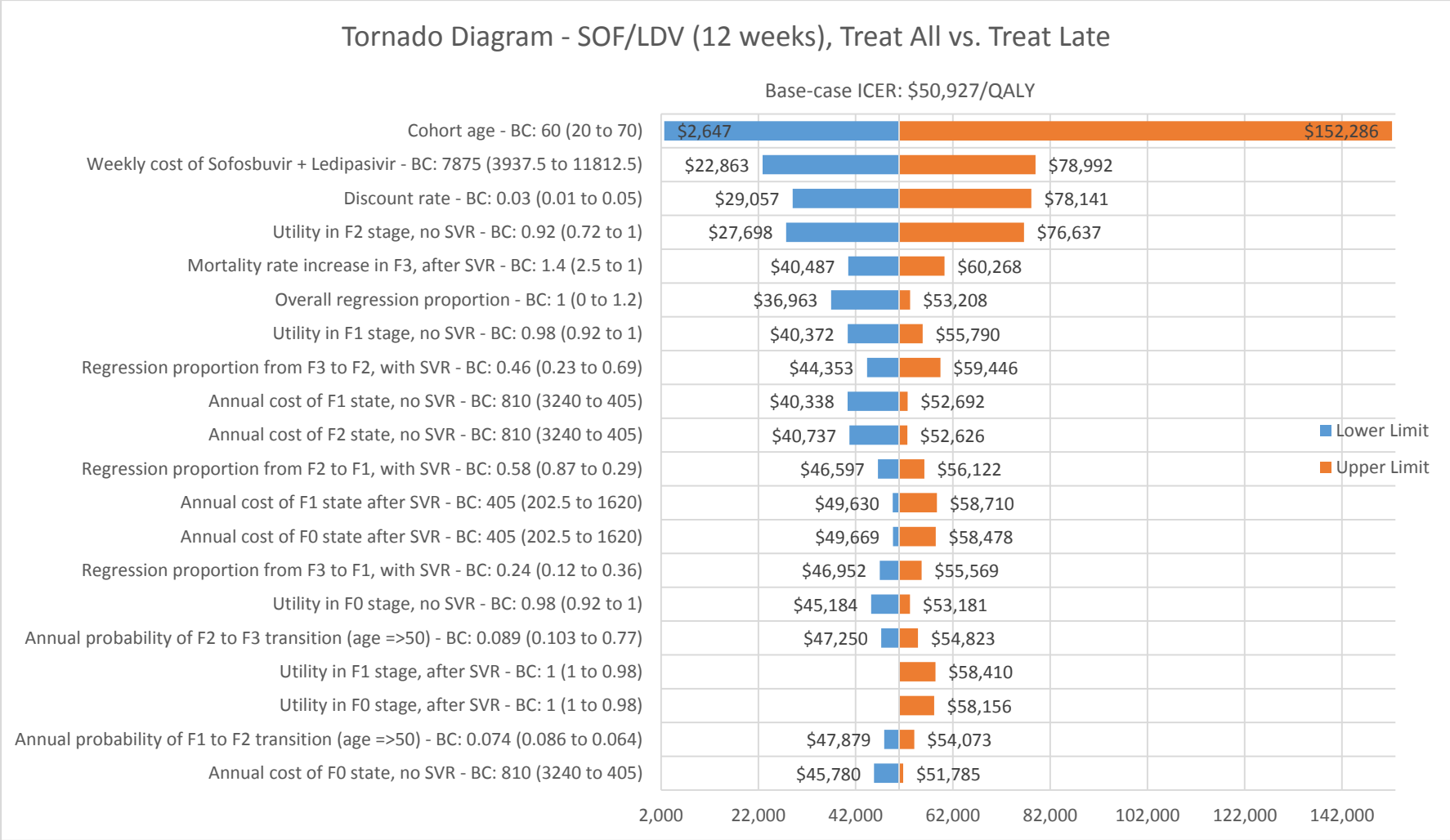
eFigure 5 Legend: A two-way sensitivity analysis of cost of simeprevir and sofosbuvir with a range of -90% to +50% of base-case value. Base-case values are $5,530/week and $7,000/week for simeprevir and sofosbuvir, respectively. The intersection of the yellow lines represents the results of the base-case analysis. The blue portion of the figure shows what the prices of both drugs would need to be in order for treating all (regardless of fibrosis stage) to be considered cost-effective compared to treating at F3/F4 ('treat late in figure legend' implies treating only when patients reach F3 and F4 fibrosis stages), at a willingness-to-pay (WTP) of $50,000/QALY. For example, one such possible combination of prices is a weekly cost of $3,000 for both drugs, represented by the intersection of two black lines. At these prices, it would be considered cost-effective to treat all versus waiting until F3 and F4 at WTP of $50,000/QALY.

4. Deterministic sensitivity analyses – Tornado diagrams



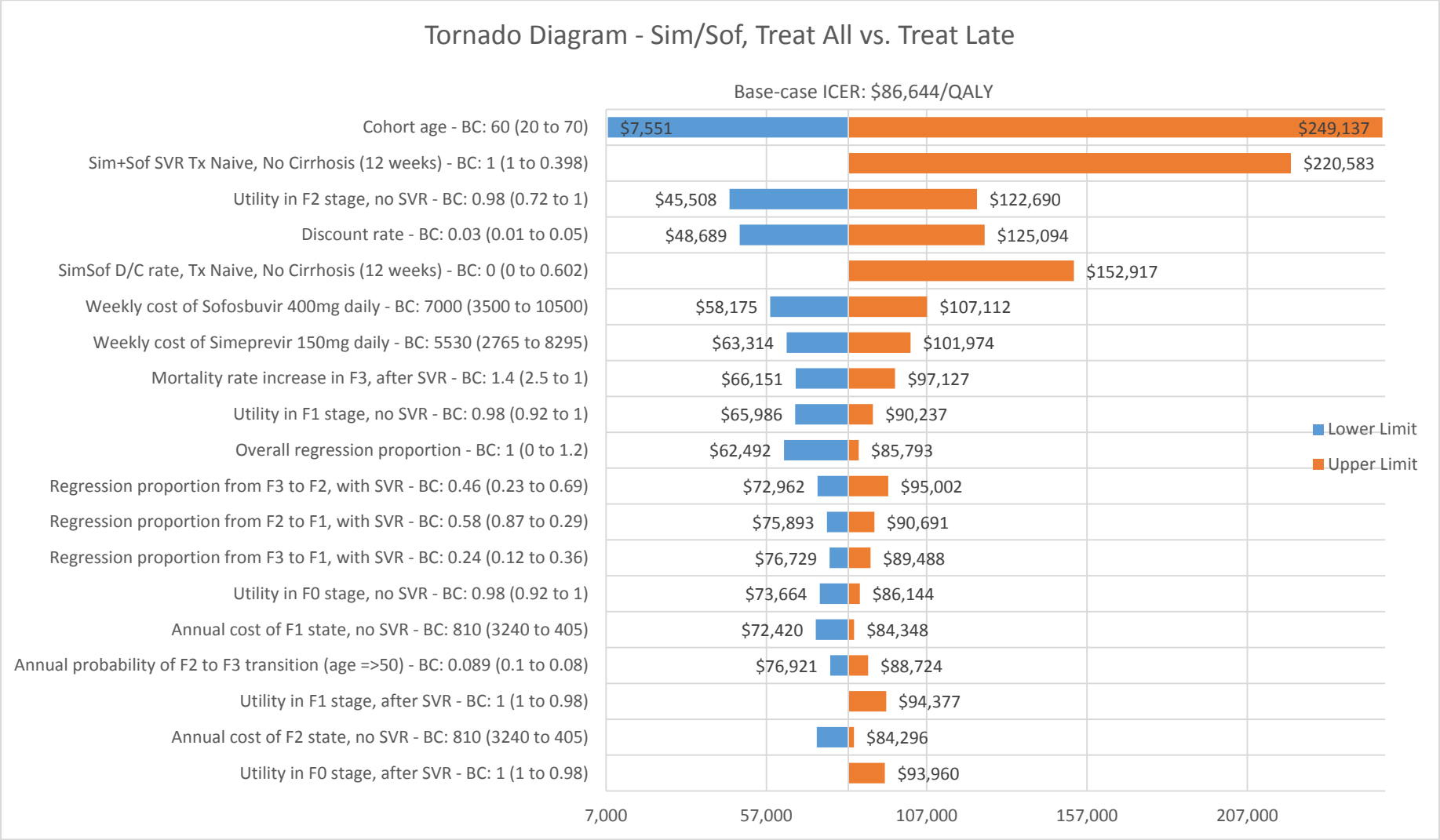
eFigure 6: Tornado diagram - ICER of 3D, treat all vs. treat at F3/F4

eFigure 6 Legend: Tornado diagram - ICER of 3D, treat all vs. treat at F3/F4. The diagram depicts one-way sensitivity analyses for the inputs with the greatest impact on the ICER. Orange bars indicate an increase in ICER relative to base-case to the upper limit of the input variable; blue bars indicate the inverse. For example, as age increases from 20 through the base-case of 60 to 70 years, the ICER increases. A high-to-low order of the range, as for annual cost of F1 health state (no SVR), indicates an inverse relationship between input value and ICER. Abbreviations: BC – base case value; F0/F1/F2/F3 – liver fibrosis stages; SVR – Sustained Virologic Response.



eFigure 7: Tornado diagram - ICER of SOF/LDV (12 weeks), treat all vs. treat at F3/F4

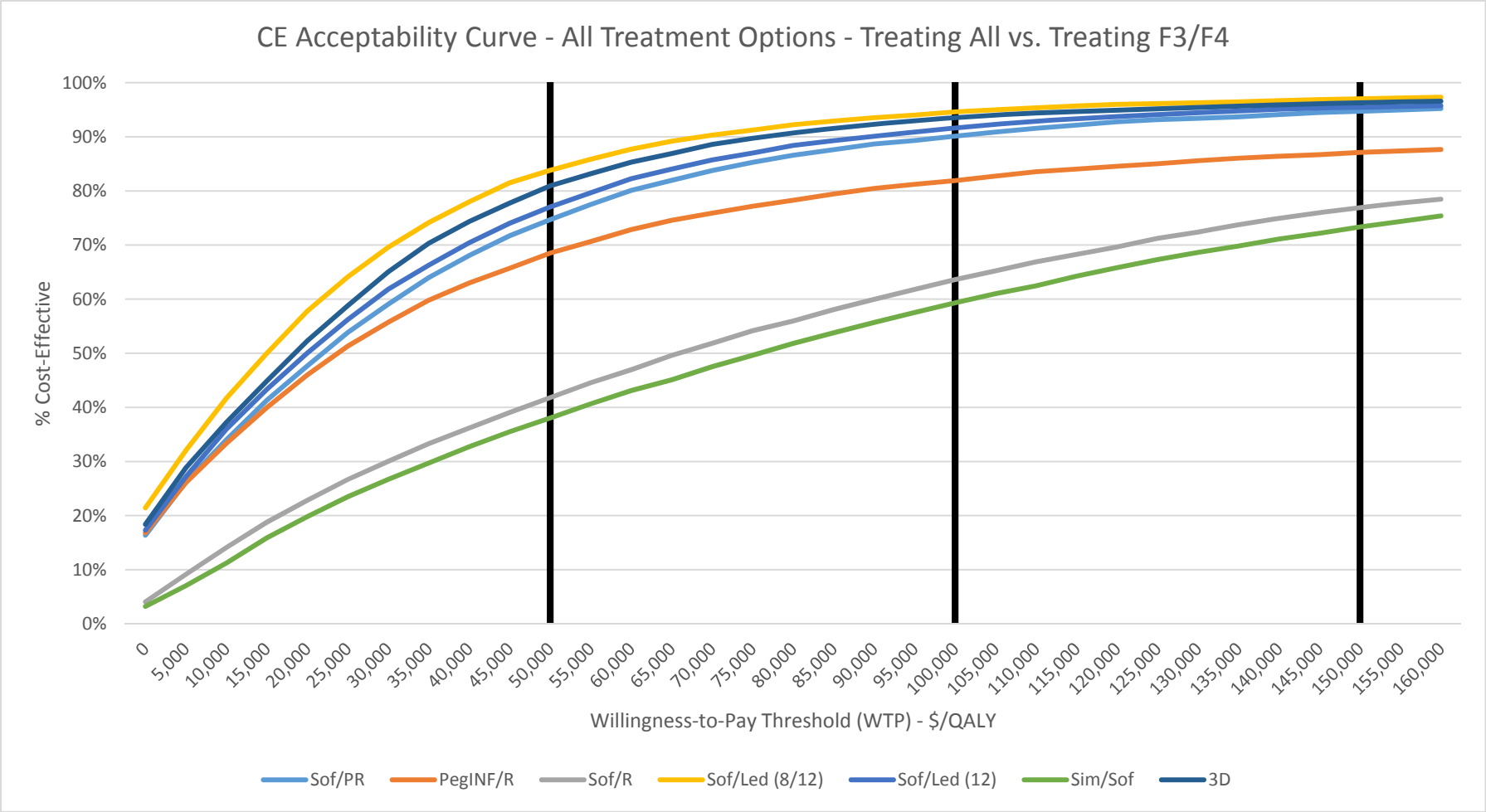
eFigure 7 Legend: Tornado diagram - ICER of SOF/LDV (12 weeks), treat all vs. treat at F3/F4. The diagram depicts one-way sensitivity analyses for the inputs with the greatest impact on the ICER. Orange bars indicate an increase in ICER relative to base-case to the upper limit of the input variable; blue bars indicate the inverse. For example, as age increases from 20 through the base-case of 60 to 70 years, the ICER increases. A high-to-low order of the range, as for annual cost of F1 and F2 (no SVR) health states, indicates an inverse relationship between input value and ICER. Abbreviations: BC – base case value; F0/F1/F2/F3 – liver fibrosis stages; SVR – Sustained Virologic Response.



eFigure 8: Tornado diagram - ICER of Sim/Sof, treat all vs. treat at F3/F4

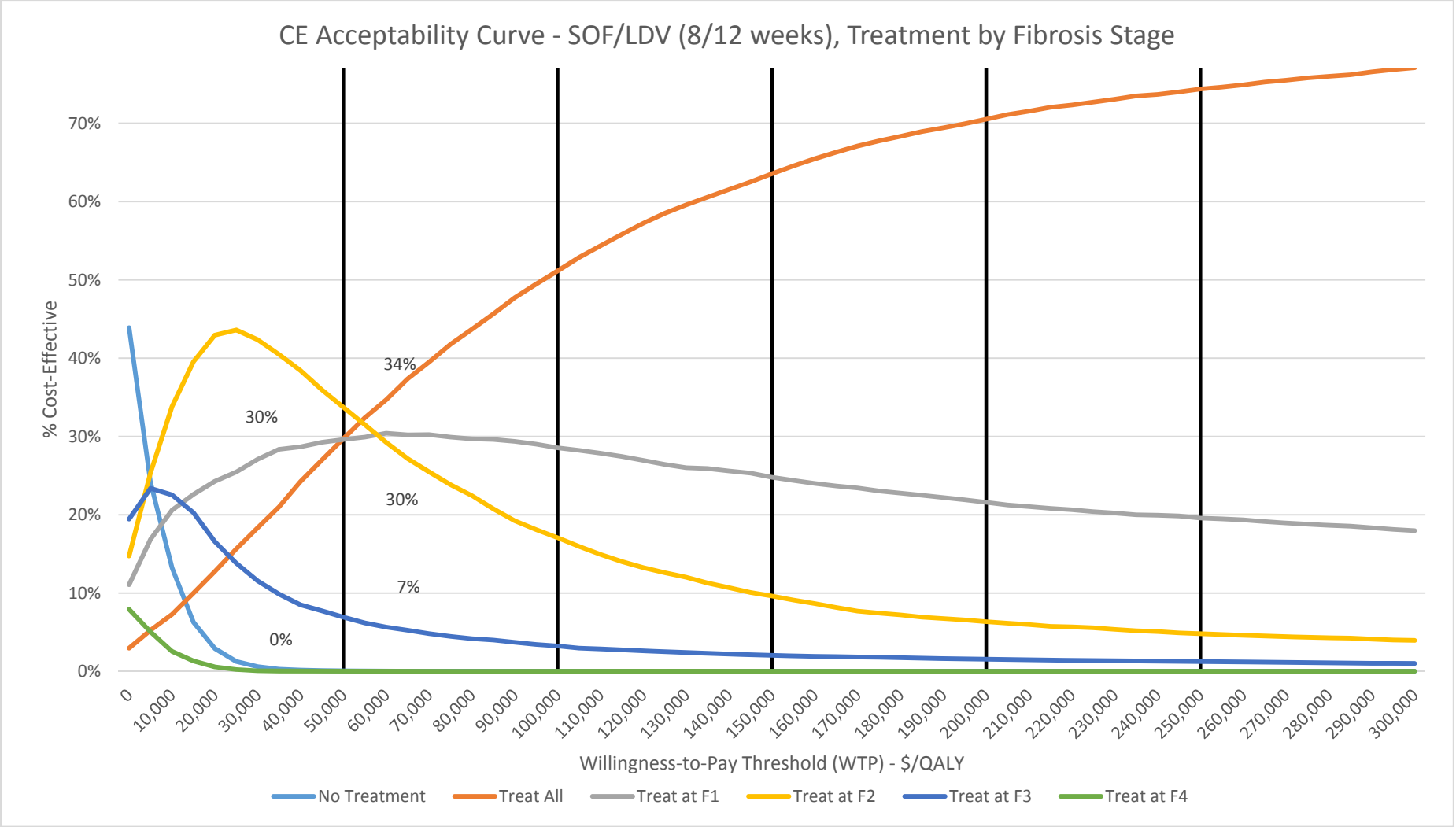
eFigure 8 Legend: Tornado diagram - ICER of Sim/Sof, treat all vs. treat at F3/F4. The diagram depicts one-way sensitivity analyses for the inputs with the greatest impact on the ICER. Orange bars indicate an increase in ICER relative to base-case to the upper limit of the input variable; blue bars indicate the inverse. For example, as age increases from 20 through the base-case of 60 to 70 years, the ICER increases. A high-to-low order of the range, as for SVR rate, indicates an inverse relationship between input value and ICER. Abbreviations: BC – base case value; F0/F1/F2/F3 – liver fibrosis stages; SVR – Sustained Virologic Response.

5. Probabilistic sensitivity analyses



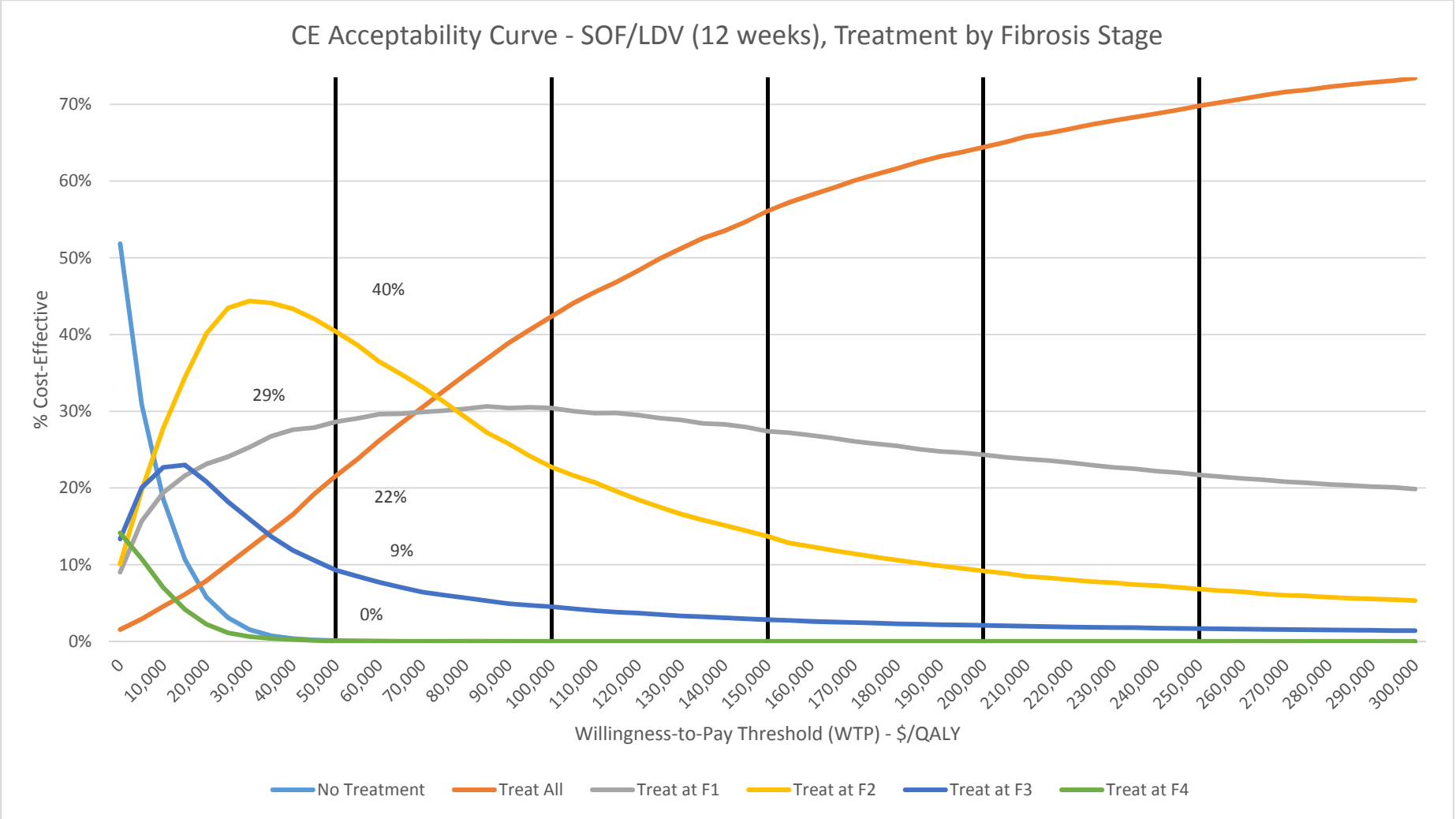
eFigure 9: Cost-effectiveness acceptability curve – All treatment options, treating all vs. treating at F3/F4

eFigure 9 Legend: Results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the listed ranges. The graph shows percent of simulation (on y-axis) in which treating all (regardless of fibrosis stage) with a given treatment option was considered cost-effective compared to treating only when patients reach fibrosis stages F3 and F4, depending on willingness-to-pay (WTP) threshold (on x-axis). As the WTP increases (from left-to-right on x-axis), the percent of simulations resulting in treating all being cost-effective also increases. For example, for treatment with SOF/LDV (8/12), at a WTP of $50,000/QALY, treating all is cost-effective about 74% of the time and at a WTP of $150,000/QALY, treating all is cost-effective about 96% of the time.



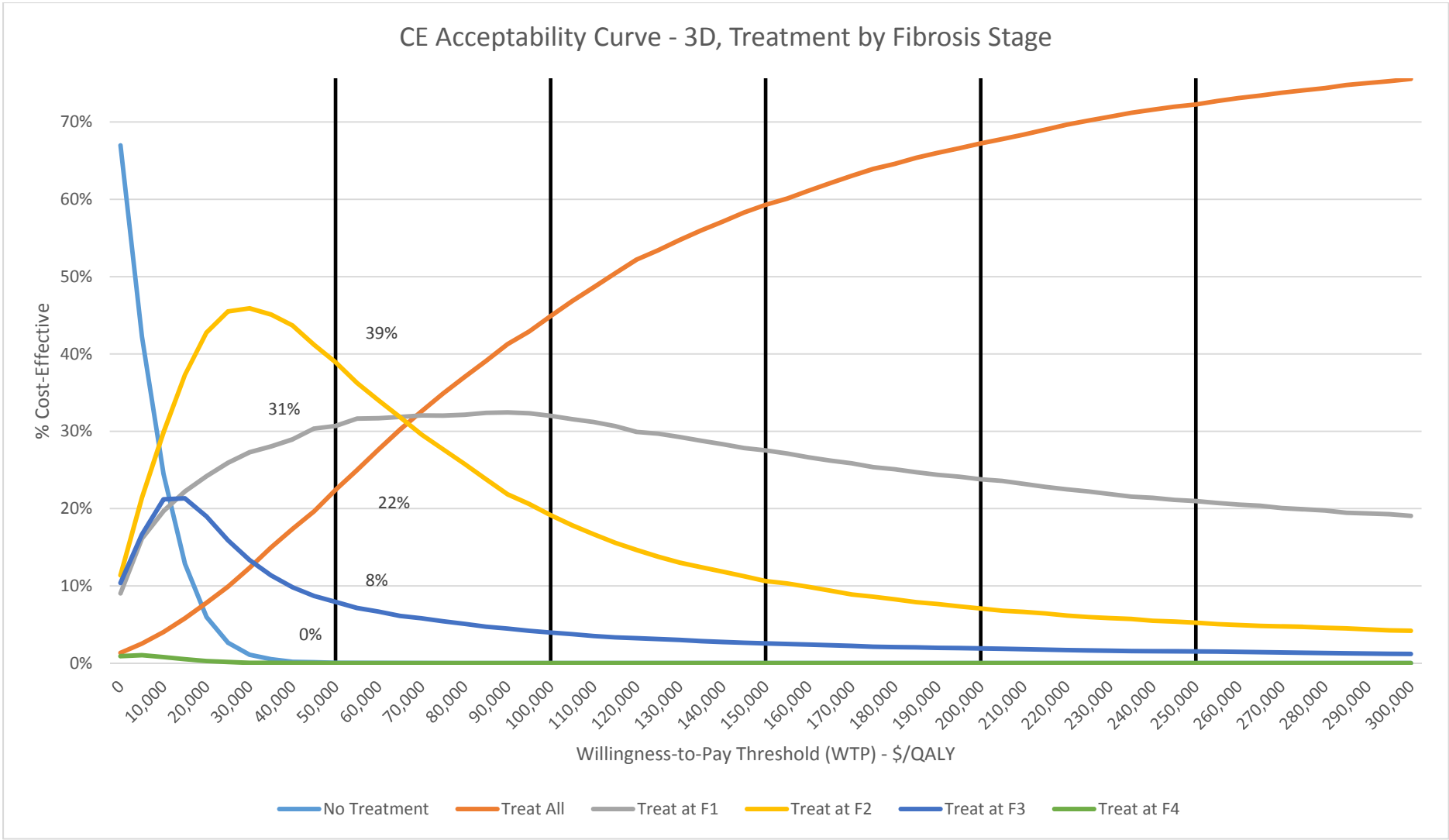
eFigure 10: Cost-effectiveness acceptability curve – SOF/LDV (8/12 weeks), treatment by fibrosis stage

eFigure 10 Legend: Results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the listed ranges. The graph shows percent of simulation (on y-axis) in which treating patients at a given fibrosis level was considered cost-effective, depending on willingness-to-pay (WTP) threshold (on x-axis). The options are to treat all (regardless of fibrosis stage), wait until F1, or until a progression to subsequent higher fibrosis stage. As the WTP increases (from left-to-right on x-axis), the percent of simulations resulting in treating all being cost-effective also increases. For example, for treatment with SOF/LDV (8/12), at a WTP of $50,000/QALY, treating at F2 is cost-effective about 34% of the time, treating all (at F0) and treating at F1 is cost-effective in 30% of the time, treating at F3 is favorable 7% of the time, while no treatment and treatment at F4 was not considered to cost-effective at all. The cumulative probability of all options at any given WTP sum to 100%.



eFigure 11: Cost-effectiveness acceptability curve – SOF/LDV (12 weeks), treatment by fibrosis stage

eFigure 11 Legend: Results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the listed ranges. The graph shows percent of simulation (on y-axis) in which treating patients at a given fibrosis level was considered cost-effective, depending on willingness-to-pay (WTP) threshold (on x-axis). The options are to treat all (regardless of fibrosis stage), wait until F1, or until a progression to subsequent higher fibrosis stage. As the WTP increases (from left-to-right on x-axis), the percent of simulations resulting in treating all being cost-effective also increases. For example, for treatment with SOF/LDV (12), at a WTP of $50,000/QALY, treating at F2 is cost-effective about 40% of the time, treating all (at F0) is cost-effective in 22% and treating at F1 is cost-effective in 29% of simulations, treating at F3 is favorable 9% of the time, while no treatment and treatment at F4 was not considered to cost-effective at all. The cumulative probability of all options at any given WTP sum to 100%.



eFigure 12: Cost-effectiveness acceptability curve – 3D, treatment by fibrosis stage

eFigure 12 Legend: Results of 10,000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the listed ranges. The graph shows percent of simulation (on y-axis) in which treating patients at a given fibrosis level was considered cost-effective, depending on willingness-to-pay (WTP) threshold (on x-axis). The options are to treat all (regardless of fibrosis stage), wait until F1, or until a progression to subsequent higher fibrosis stage. As the WTP increases (from left-to-right on x-axis), the percent of simulations resulting in treating all being cost-effective also increases. For example, for treatment with 3D, at a WTP of $50,000/QALY, treating at F2 is cost-effective about 39% of the time, treating all (at F0) is cost-effective in 22% and treating at F1 is cost-effective in 31% of simulations, treating at F3 is favorable 8% of the time, while no treatment and treatment at F4 was not considered to cost-effective at all. The cumulative probability of all options at any given WTP sum to 100%.

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