Appraisal Consultation Document – Sofosbuvir for treating chronic hepatitis C

Gilead response to further analysis required by the Appraisal Committee – June 2014

1. Scenario 1: TPs from Cardoso + Utility from Vera-Llonch + Mortality rates + Ribavirin cost

As requested by the Appraisal Committee the cost-effectiveness model was re-run (from now onwards the new model is referred to as "Scenario analysis model" and the submitted model as "Base case model") with the following parameters changed:

- Transition probabilities (TPs) from compensated cirrhosis with and without SVR to hepatocellular carcinoma (HCC) from Cardoso et al. (2010)[1], that is, 0.0128 and 0.0631, respectively.[2]
- Utility increment after reaching sustained virological response (SVR) of 0.041 from Vera-Llonch et al. (2013)[3]
- Probability of death re-estimated assuming the distribution between male and female from Wright et al. (2006) (61% male and 39% female)[4,5]

  Average cost for generic ribavirin (RBV) based on eMIT: £42.50 for a 56-tablet pack size.[6]

The incremental cost-effectiveness ratios per quality-adjusted life year (ICERs/QALY) gained for genotype (GT) 1 and GT3 are presented for both the Base case model and the Scenario analysis model in Table 1 for a combined cohort and in Table 2 for a cohort of non-cirrhotic and cirrhotic patients. These show that ICERs/QALY gained did not change substantially from those initially submitted. The corresponding probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) are shown in 5.b.

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[1] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52(5):652–657.

[2] In the Base case model the TP from cirrhotic without SVR to HCC was obtained from Fattovich et al. (1997). However, since Fattovich et. al (1997) did not report a TP from cirrhotic with SVR to HCC we considered it more appropriate to use both TPs from Cardoso et al. (2010)

[3] Vera-Llonch M, Martin M, Aggarwal J, et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013; 38: 124–33.

[4] Death Registrations Summary Statistics, England and Wales, 2011, table 1 - Death rates by age and sex, 2001, 2010 and 2011, Office for National Statistics

[5] Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006; 10:1-113.

[6] eMIT, 02/2014, NPC: DEC223, Ribavirin 400 mg tablets/Packsize 56

Table 1 – ICERs/QALY for GT1 and GT3: combined cohort (Scenario analysis model versus Base case model)

Indication	Treatment strategies	ICERS (£/QALY) Base case model	ICERS (£/QALY) Scenario analysis model
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	11,836	15,396
	SOF+PR vs. BOC+PR (RGT)	7,292	10,335
	SOF+PR vs. PR (48 wks)	14,930	17,476
GT1 TN UI	SOF+RBV* vs. NT	49,249	47,611
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	21,860
GT3 TN UI	SOF+RBV vs. NT	21,478	21,049
GT3 TE IE	SOF+PR (12 wks) vs. NT	8,557	9,006
	SOF+PR (12 wks) vs. PR (48 wks)	12,246	13,883
GT3 TE UI	SOF+RBV vs. NT	28,569	27,483

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a/b + RBV; RBV: Ribavirin; RGT: Response guided therapy; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

**note: section 4.4 of the SOF SmPC states that 'SOF/RBV for 24 wks in GT1UI should only be used for patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment'. With the recent interim NHS England commissioning policy advocating use of SOF + Daclatasvir/Ledipasvir (for compassionate use) it is anticipated that this regimen would only be used in highly exceptional circumstances.*

Table 2 – ICERs/QALY for GT1 and GT3: non-cirrhotic and cirrhotic cohorts (Scenario analysis model versus Base case model)

		ICERS (£/QALY) Base case model		ICERS (£/QALY) Scenario analysis model	
Indication	**Treatment strategies**	**Non-cirrhotic cohort**	**Cirrhotic cohort**	**Non-cirrhotic cohort**	**Cirrhotic cohort**
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	18,819	846	22,304	4,253
	SOF+PR vs. BOC+PR (RGT)	11,471	-500	14,280	2,819
	SOF+PR vs. PR (48 wks)	23,119	2,433	25,237	5,352
GT1 TN UI	SOF+RBV vs. NT	53,841	35,258	51,478	35,754
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	42,240	4,281	40,623	6,556
GT3 TN UI	SOF+RBV vs. NT	30,119	8,936	28,044	10,505
GT3 TE IE	SOF+PR (12 wks) vs. NT	13,645	1,271	12,888	3,197
	SOF+PR (12 wks) vs. PR (48 wks)	17,960	3,539	18,592	6,260
GT3 TE UI	SOF+RBV vs. NT	33,777	17,983	31,416	19,179

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a/b + RBV; RBV: Ribavirin; RGT: Response guided therapy; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

The new analyses are deemed extremely conservative for the following reasons.

- First and most importantly the primary factor driving increased ICERs/QALY in the scenario analysis model is the use of a generic RBV price. Whilst we have incorporated the respective price of generic RBV from the eMIT website as requested by the Committee, we would like to highlight that according to the MHRA website, 'generic RBV should only be used as part of a combination with interferon or peginterferon alfa-2b'. Furthermore market share data based on UK IMS hospital and retail sales at April 14 MAT confirms that unbranded RBV accounts for less than 3% of total UK market share. Generic RBV should therefore not be considered the standard RBV of choice due to its low market share and restrictions for use in combination with peginterferon alfa-2a.

- Secondly, the utility from Vera-Llonch et al. (2013) is lower than that used in the model from Wright et al. (2006) (0.041 versus 0.05). The latter being the most cited, widely used and accepted source for utility increment. Wright et al. (2006) was also accepted in all previous health technology assessment (HTA) submissions. Moving away from this previously accepted transition probability unfairly discriminates against regimens which have improved SVR rates.
- The Committee also requested the utility increment for patients that reached SVR to be taken from the sofosbuvir clinical trials. This is not appropriate since patients were not aware of SVR status when completing SF36. Despite this, some improvement in health-related quality of life was reported[7]. This was also noted in section 3.24 of the ACD.

The Base case model also considered patients who started treatment at either 40 or 45 years of age. This age range was also used by Hartwell et al. (2011)[8] and is believed to reflect the characteristics of patients with HCV in the UK. The Committee requested a sensitivity analysis assuming patients start treatment at the ages of 35 and 55. Results are presented in Table 3 for a combined cohort of non-cirrhotic and cirrhotic patients. We can conclude that the impact of age at treatment start on the ICERs is not substantial. In addition, with the advent of new interferon sparing treatments it is likely that patients will initiate treatment much earlier and based on this analysis starting treatment at 35 years of age is more cost-effective compared with ages of 40 to 45 and 55.

Table 3 – ICERs/QALY for a combined cohort with age 35 and 55

Indication	Treatment strategies	ICERs(£/QALY)			
		Base case model	Scenario analysis model: Age 40-45	Scenario analysis model: Age 35	Scenario analysis model: Age 55
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	11,836	15,396	14,648	18,255
	SOF+PR vs. BOC+PR (RGT)	7,292	10,335	9,993	12,164
	SOF+PR vs. PR (48 wks)	14,930	17,476	16,510	20,900
GT1 TN UI	SOF+RBV vs. NT	49,249	47,611	46,853	53,911
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	21,860	22,479	28,359
GT3 TN UI	SOF+RBV vs. NT	21,478	21,049	19,908	23,114
GT3 TE IE	SOF+PR (12 wks) vs. NT	8,557	9,006	8,560	9,888
	SOF+PR (12 wks) vs. PR (48 wks)	12,246	13,883	13,001	15,648
GT3 TE UI	SOF+RBV vs. NT	28,569	27,483	26,297	29,660

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a/b + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; RGT: Response guided therapy; SOF: Sofosbuvir; SVR: Sustained virological response; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

2. Scenario 2: SVR rates from Hadziyannis et al.

The Appraisal Committee requested a scenario analysis using the SVR rates from Hadziyannis et al. (2004)[9] for peginterferon alfa and ribavirin (PR) in GT1 treatment-naïve (TN) patients. We have concerns regarding this approach because the SVR rates in

[7] Younossi et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). Journal of Hepatology 2014

[8] Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011; 15:i-210.

[9] Hadziyannis SJ, Sette J, Morgan TR, Balan V, Diago M, Marcellin P et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140(5):346-355.

Hadziyannis et al. (2004) are reported for F0-F2 and F3-F4 METAVIR scores. This offers significant bias against SOF since in the NEUTRINO trial, non-cirrhotic and cirrhotic patients were defined as F0-F3 and F4, respectively. In the Base case model, SVR rates from McHutchison et al. (2009)[10] were used. Clinical expert opinion deemed McHutchison et al. (2009) as the most appropriate source since it is the largest (1035 vs. 271 patients in Hadziyannis et al), most recent publication and is also commonly cited as being the most representative of current treatment practice and outcomes. It should also be noted that compared with the Hadziyannis study the patients in the McHutchison study were older (48 years vs. 43 years), heavier (82.8kg. vs. 77.3kg) and with a higher proportion of patients with black ethnicity (19% vs. 3%), thus being most representative of the population seen within the Neutrino trial for GT1.

Given all the above we believe that the most appropriate source is McHutchison et al. (2009). However, we have conducted the analyses requested with results presented in Table 4, which show a slight increase in the ICERs/QALY gained when the SVR rates from Hadziyannis et al. (2004) are used. Please note that for comparison we also included the ICERs/QALY obtained using the SVR rates from McHutchison et al. (2009) and the ICERs/QALY from the base case model for these two publications.

PSA results for the analysis with Hadziyannis et al. (2004) are provided in appendix 5.c.

Table 4 – ICERs/QALY GT1 TN versus PR

	ICERs(£/QALY)		
	Combined cohort	**Non-cirrhotic cohort**	**Cirrhotic cohort**
Base case model with SVRs from McHutchison et al. (2009)	14,930	23,119	2,433
Base case model with SVRs from Hadziyannis et al. (2004)	21,857	32,167	5,819
Scenario analysis model with SVRs from McHutchison et al. (2009)	17,476	25,237	5,352
Scenario analysis model with SVRs from Hadziyannis et al. (2004)	25,014	34,928	9,112

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life years; SVR: Sustained virological response

3. Scenario 3: SOF+RBV for 24 weeks for GT3 TN/TE

Table 5 and Table 6 present ICERs/QALY gained for the recommended SOF regimens for GT3 patients. As mentioned previously, ICERs/QALY from the Scenario analysis model do not substantially differ from those initially submitted in the Base case model.

Table 5 – ICERs/QALY for GT3: combined cohort (Scenario analysis model versus Base case model)

Indication	Treatment strategies	ICERS (£/QALY) Base case model	ICERS (£/QALY) Scenario analysis model
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	21,860
GT3 TN UI	SOF+RBV (24 wks) vs. NT	21,478	21,049
GT3 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	12,246	13,883
GT3 TE UI	SOF+RBV (24 wks) vs. NT	28,569	27,483

[10] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffmann R et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009; 360:1827-1838

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: Weeks

Table 6 – ICERs/QALY for GT3: non-cirrhotic and cirrhotic cohorts (Scenario analysis model versus Base case model)

		ICERS (£/QALY) Base case model		ICERS (£/QALY) Scenario analysis model	
Indication	**Treatment strategies**	**Non-cirrhotic cohort**	**Cirrhotic cohort**	**Non-cirrhotic cohort**	**Cirrhotic cohort**
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	42,240	4,281	40,623	6,556
GT3 TN UI	SOF+RBV (24 wks) vs. NT	30,119	8,936	28,044	10,505
GT3 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	17,960	3,539	18,592	6,260
GT3 TE UI	SOF+RBV (24 wks) vs. NT	33,777	17,983	31,416	19,179

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: Weeks

The recommended and licensed regimen for patients who are interferon eligible is 12 weeks of SOF + PR. Nevertheless, and in response to a request from the Appraisal Committee the following two scenario analyses were conducted:

1. A scenario analysis assuming that 100% of patients who are interferon eligible will receive 24 weeks of SOF + RBV vs. PR was performed.

Results are presented in Table 7. As expected the longer treatment duration resulted in higher ICERs/QALY gained. We do not believe this is a relevant comparison. For GT3 we had originally submitted ICERs/QALY for SOF+PR (12wks) vs PR and SOF+RBV (24 wks) vs. NT as an option only for those that are deemed unsuitable for interferon based therapies.

We are not requesting, nor do we anticipate any patients who are able to tolerate PR would be given the option of the 24 week interferon-free sofosbuvir regimen in preference to the more effective and shorter 12 week interferon-containing option.

Clinical opinion has further confirmed this position with most clinicians choosing the 12 week interferon-containing regimen unless there are absolute medical contraindications to using interferon in their patients.

Table 7 – ICERs/QALY for GT3 IE assuming SOF+RBV for 24 weeks (Scenario analysis model versus Base case model)

		ICERS (£/QALY) Base case model			ICERS (£/QALY) Scenario analysis model		
Indication	**Treatment strategies**	**Combined cohort**	**Non-cirrhotic cohort**	**Cirrhotic cohort**	**Combined cohort**	**Non-cirrhotic cohort**	**Cirrhotic cohort**
GT3 TN IE	SOF+RBV (24 wks) vs. PR (24 wks)	46,713	106,843	12,839	46,956	100,227	14,853
GT3 TE IE	SOF+RBV (24 wks) vs. PR (48 wks)	48,687	49,621	45,814	48,306	47,992	49,341

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

2. A second scenario analysis was investigated (based upon the upper and lower variance offered by the clinical experts engaged by the ERG [ACD section 3.58]) by assuming that either 98% or 80% of patients receive triple therapy for 12 weeks, and 2% or 20% receive dual therapy for 24 weeks, respectively vs. PR. Results are presented in Table 8 and show that SOF offers cost-effective regimens in a cohort of GT3 TN (at a

£30,000/QALY threshold) and treatment-experienced (TE) patients (at a £20,000/QALY threshold) that are representative of current disease distribution in the UK.

Table 8 – ICERs/QALY for GT3 IE: combination of SOF+PR for 12 weeks and SOF+RBV for 24 weeks

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model		
		Combined cohort	Non-cirrhotic cohort	Cirrhotic cohort
GT3 TN IE	98% SOF+PR (12 wks) + 2% SOF+RBV (24 wks)	22,385	41,669	6,752
	80% SOF+PR (12 wks) + 20% SOF+RBV (24 wks)	27,062	51,327	8,452
GT3 TE IE	98% SOF+PR (12 wks) + 2% SOF+RBV (24 wks)	14,467	19,209	6,707
	80% SOF+PR (12 wks) + 20% SOF+RBV (24 wks)	19,890	24,706	11,169

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

4. Scenario 4: HCV/HIV co-infected

As per HCV mono-infected patients and aligned to sofosbuvir's license, the preferred regimen for HCV/HIV co-infected patients is SOF + PR (12 weeks) unless patients are unsuitable for interferon. Table 9 details the SVR rates for HCV/HIV co-infected patients and HCV mono-infected patients treated with 12 or 24 weeks of SOF + RBV within each genotype. SVR rates for HCV mono-infected patients versus HCV/HIV co-infected patients were 68% versus 76% (GT1 treated with SOF + RBV for 24 weeks), 56% versus 67% (GT3 treatment naïve, treated with SOF + RBV for 12 weeks - unlicensed regimen) and 85% versus 92% (GT3 treatment-experienced, treated with SOF + RBV for 24 weeks, respectively. This table was presented in our response to the ERG report.

It should also be noted that current treatment guidelines recommend that HCV/HIV co-infected patients should be treated the same as mono-infected patients and the recently published '2014 EASL (European Association of the Study of the Liver) Recommendations on the Treatment of Hepatitis C' highlights the following:

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (Recommendation A1)
- The same treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1)
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (Recommendation A2)

Please note that the British HIV Association Guidelines for HCV/HIV co-infection are currently being updated to reflect a similar position to the European guidelines.

Table 9 – Comparison of SVR rates for sofosbuvir between mono- and co-infected patients

Trial	Genotype	TN/TE	Regimen	Duration (weeks)	Number of patients achieving SVR12	SVR12 Response (%)
PHOTON-1**	GT1	TN	SOF+RBV	24	87/114	76
SPARE	GT1	TN	SOF+RBV	24	17/25	68
PHOTON-1**	GT2	TN	SOF+RBV	12	23/26	88
VALENCE	GT2	TN	SOF+RBV	12	68/73	93
PHOTON-1**	GT3	TN	SOF+RBV*	12	28/42	67
FISSION	GT3	TN	SOF+RBV*	12	102/183	56
PHOTON-1**	GT3	TE	SOF+RBV	24	12/13	92
VALENCE	GT3	TE	SOF+RBV	24	212/250	85
STUDY 1910**	GT1	TN	SOF+PR	12	17/19	90
NEUTRINO	GT1	TN	SOF+PR	12	262/292	90

**Unlicensed regimens, **co-infected patients*

Since the initial submission, additional data from study 1910[11] has become available and we have provided this for information. This information was also previously provided, with the agreement of NICE, in response to the ERG clarification queries. SVR rates for HCV mono-infected patients versus HCV/HIV co-infected patients were 90%, reinforcing that similar response rates were seen in HCV/HIV co-infected patients as HCV mono-infected patients treated with SOF + PR in GT1 patients. Table 10 shows the ICERs/QALY gained for SOF + PR against PR using the data from 1910 for a non-cirrhotic cohort. As can be observed below, SOF + PR given for 12 weeks remains a cost-effective treatment option for GT1 HCV/HIV co-infected patients.

Table 10 – ICERs/QALY for GT1 HCV/HIV co-infected with data from 1910

Indication	Treatment strategies	ICERS (£/QALY) Base case model	Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR	14,745	15,866

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

We would also like to stress again that the ICERs originally submitted in the appendices for GT3 HCV/HIV co-infected patients used data from the PERICO trial. These data presented a few limitations:

- First, the SVR rate (86%) was reported for all patients but not for non-cirrhotic and cirrhotic patients separately. Therefore an assumption had to be made that the SVR rate of 86% applied to the non-cirrhotic cohort. An adjustment based on Laguno et al. (2009)[12] was then applied to obtain the SVR rate for cirrhotic patients of 61%. Given that co-infected patients are expected to have response rates similar to mono-infected patients, the SVR rate of 61% for the cirrhotic population is likely to be inflated. For instance, we estimated a SVR rate of 35% for mono-infected cirrhotic

[11] Rodriguez-Torres M, Rodriguez-Orengo JF, Gaggar A, et al. Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1-4 HCV-Infected Patients Who Are Coinfected With HIV. 53rd ICAAC 2013. Sept 10-13, 2013, 2013; Denver, CO

[12] Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras A et al. Randomized trial comparing pegylated interferon -2b versus pegylated interferon -2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology 2004; 49:22-31.

patients based on the publication by Lagging et al (2013)[13] and the distribution between relapsers and non-responders from Shoeb et al (2011)[14]

- Second, the SVR rates for TE patients were assumed to be the same as those for TN patients (as mentioned previously, 86% and 61% for non-cirrhotic and cirrhotic patients, respectively) as no data was available for this population in the TE indication. This is considered to be a big limitation since a significant difference has been observed in the SVR rates between TN and TE in mono-infected patients. Had we used a more conservative estimate such as Lagging et al (2013) and Shoeb et al (2011), this would have resulted in similar ICERs to those seen in the mono-infected population. However, at the time of the analysis no publication was found that provided efficacy data on TE HCV/HIV co-infected patients. Consequently, we have conducted a further scenario analysis assuming a more likely scenario for the TE population using SVR rates from Lagging et al. (2013) and Shoeb et al (2011). These are presented in table 10.

In summary, as highlighted in the 2014 EASL guidelines (recommendation A1) and supported by the results from our trials (see Table 9) we believe the HCV/HIV co-infected population responds in a similar manner to the mono-infected population.

Table 11 lists the ICERs from all sofosbuvir trial data available for HCV/HIV co-infection aligned to the final licensed regimens for GT1 and GT3 from the summary of product characteristics (SmPC). That is 12 weeks SOF + PR [1910] or 24 weeks SOF + RBV for the TE population [Photon 1[15]]. The respective PSA results are presented in appendix 5.d.

Table 11 – ICERs/QALY for HCV/HIV co-infected

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR (data for SOF from trial 1910)	15,866
	SOF+RBV (24 wks) vs. NT	27,059
GT3 TE	SOF+RBV (24 wks) vs. PR (SVR for PR from Lagging and Shoeb)*	17,167
	SOF+RBV (24 wks) vs. NT	10,376

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; NT: No treatment; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

**Whilst we have included ICERs for the 24wk SOF + RBV regimen vs PR in GT3 TE as requested by the Committee, we are not requesting, nor do we anticipate (as with the mono-infected population) any patients who are able to tolerate PR would be given the option of the 24 week interferon-free sofosbuvir regimen in preference to the more effective and shorter 12 week interferon-containing option*

5. Appendices

a. Impact of changing each parameter individually

The impact of changing each of the requested parameters individually was also investigated. ICERs/QALY are presented in Table 12 and show that the cost of RBV and the utility increment after reaching SVR have the biggest impact in the analyses. However, conclusions around the cost-effectiveness of sofosbuvir remain the same to those in the Base case model.

[13] Lagging M, Rembeck K, Buhl MR et al. Retreatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scandinavian journal of gastroenterology 2013;48:839-847.

[14] Shoeb D, Rowe IA, Freshwater D et al. Response to antiviral therapy in patients with genotype 3 chronic hepatitis C: fibrosis but not race encourages relapse. *Eur J Gastroenterol Hepatol* 2011;23:747-753

[15] Sulkowski M et al., All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1). 64th Annual Meeting of the American Association for the Study of Liver diseases, November 1-5, 2013, Washington, SA; oral abstract 212

Table 12 – ICERs/QALY for GT1 and GT3 on the combined cohort

Indication	Treatment strategies	Base case model	TP from Cardoso et al. (2010)	ICERS (£/QALY) Mortality distribution from Wright et al. (2006)	RBV cost	Utility from Vera-Llonch et al. (2013)
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	11,836	11,884	11,985	14,353	12,787
	SOF+PR vs. BOC+PR (RGT)	7,292	7,550	7,400	9,433	7,899
	SOF+PR vs. PR (48 wks)	14,930	14,748	15,113	16,463	16,097
GT1 TN UI	SOF+RBV vs. NT	49,249	44,870	49,774	47,843	53,793
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	20,546	20,808	20,736	21,791
GT3 TN UI	SOF+RBV vs. NT	21,478	20,306	21,728	20,765	22,960
GT3 TE IE	SOF+PR (12 wks) vs. No treatment	8,557	8,726	8,682	8,187	9,156
	SOF+PR (12 wks) vs. PR (48 wks)	12,246	12,182	12,407	13,066	13,103
GT3 TE UI	SOF+RBV vs. No treatment	28,569	26,377	28,893	27,680	30,661

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a/b + RBV; RBV: Ribavirin; RGT: Response guided therapy; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

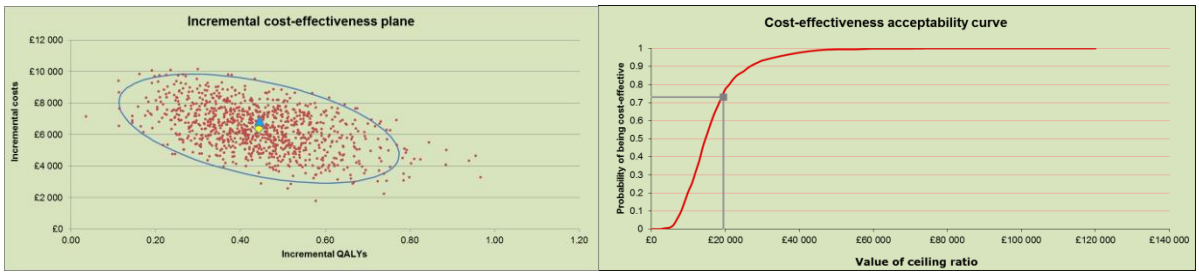
b. PSA results: Scenario 1

In addition to the input changes requested and ran for scenario 1, the assumptions around the distributions of the costs of drugs in the PSA were changed. In the original model, the treatment costs were varied +/- 25% from the base case for sofosbuvir and +/-10% for all the others treatments, using a uniform distribution. In the new model, only a -10% variation has been considered since under the Pharmaceutical Price Regulation Scheme (PPRS), drug prices can only go down.

As the drug costs are one of the main drivers of the total costs in the model, we considered it important to conduct this modification to better reflect drug cost variation in the UK.

Furthermore when looking at the isolated impact of the changes requested in scenario 1, it can be observed that the utility after reaching SVR from Vera-Llonch increases the probability that sofosbuvir is cost-effective. This is because the uncertainty associated with this utility is significantly lower than that from Wright et al. (2006) (0.01 versus 0.045).

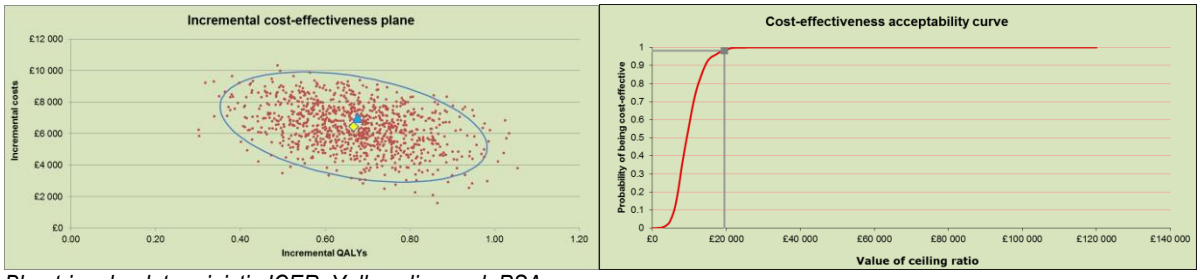
Figure 1 – PSA results for GT1 TN IE: SOF+PR (12 weeks) vs. TPV+PR



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 73% and 93% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with telaprevir.

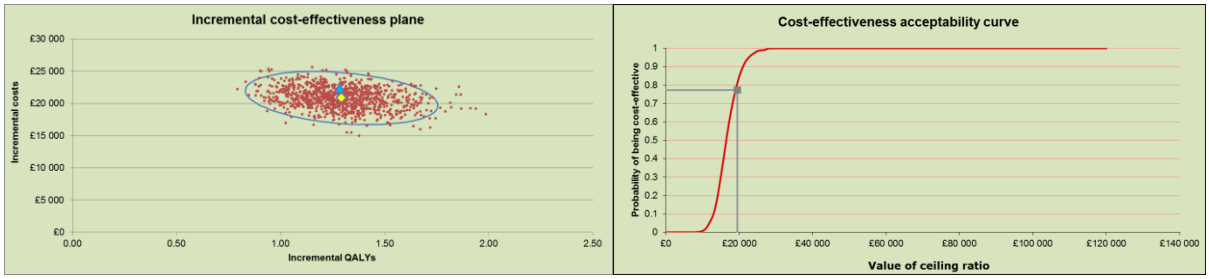
Figure 2 – PSA results for GT1 TN IE: SOF+PR (12 weeks) vs. BOC+PR



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 99% and 100% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with boceprevir.

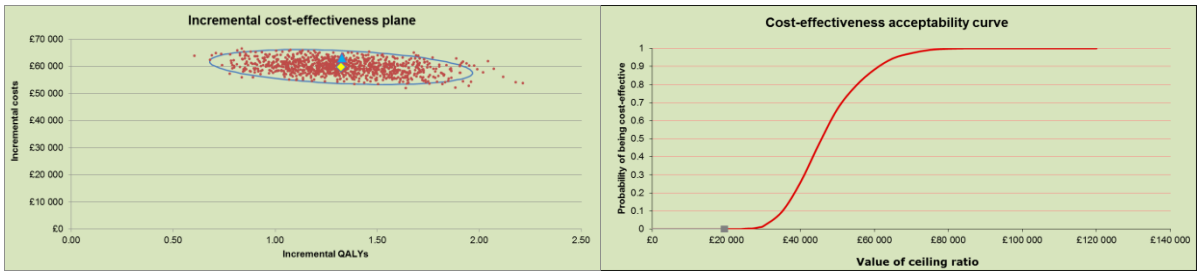
Figure 3 – PSA results for GT1 TN IE: SOF+PR (12 weeks) vs. PR (48 weeks)



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 77% and 100% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

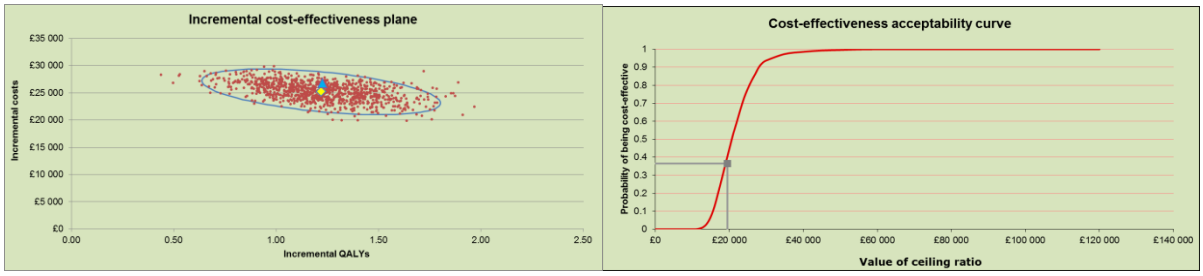
Figure 4 – PSA results for GT1 TN UI: SOF+RBV (24 weeks) vs. No treatment



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN UI patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 0% and 2% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

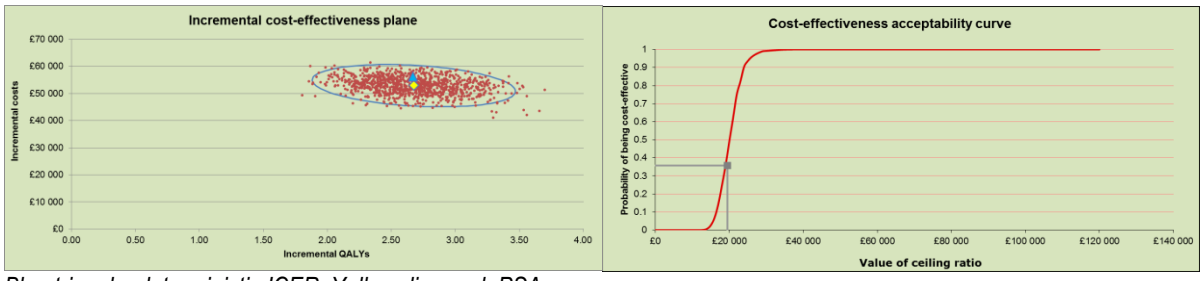
Figure 5 – PSA results for GT3 TN IE: SOF+PR (12 weeks) vs. PR (24 weeks)



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 37% and 94% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 24 weeks.

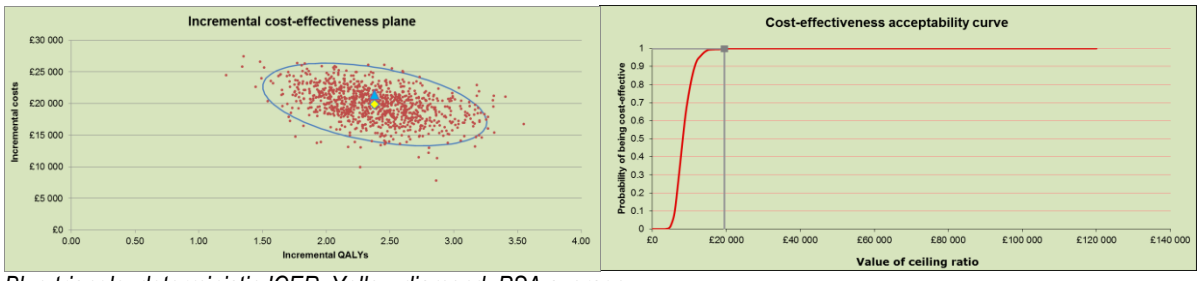
Figure 6 – PSA results for GT3 TN UI: SOF+RBV (24 weeks) vs. No treatment



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TN UI patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 36% and 99% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

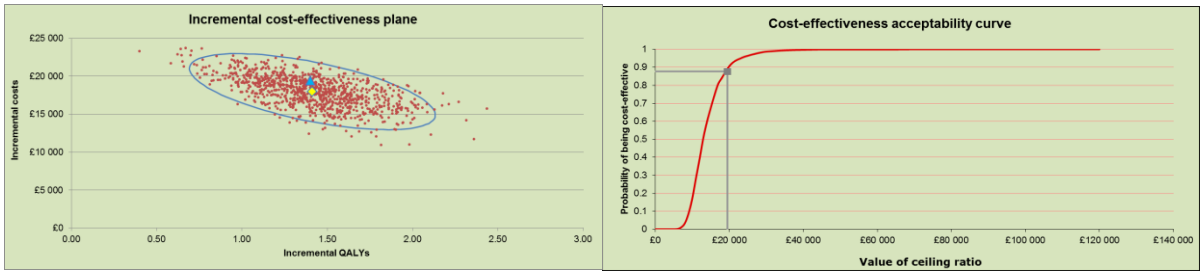
Figure 7 – PSA results for GT3 TE IE: SOF+PR (12 weeks) vs. No treatment



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TE IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 100% and 100% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

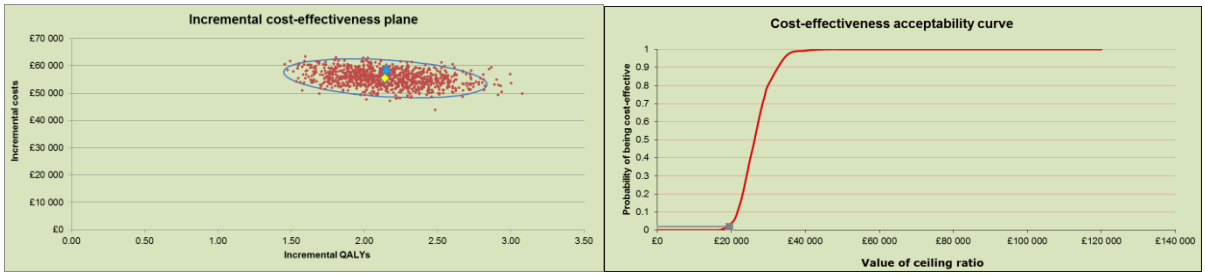
Figure 8 – PSA results for GT3 TE IE: SOF+PR (12 weeks) vs. PR (48 weeks)



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TE IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 88% and 99% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

Figure 9 – PSA results for GT3 TE UI: SOF+RBV (24 weeks) vs. No treatment

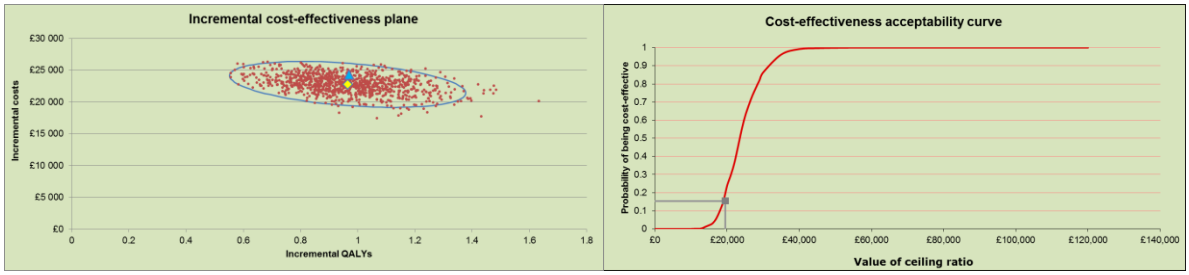


Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TE UI patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 1% and 81% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

c. PSA results: Scenario 2

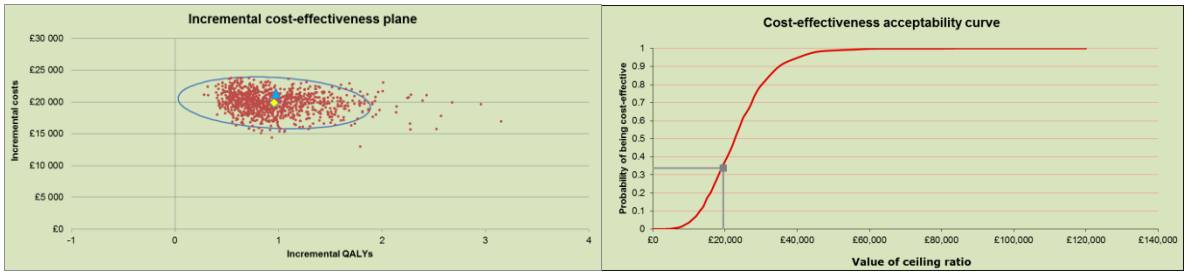
Figure 10 – PSA results for GT1 TN IE in Scenario analysis model: SOF+PR (12 weeks) vs. PR (48 weeks) with SVR from Hadziyannis et al. 2004



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 15% and 86% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

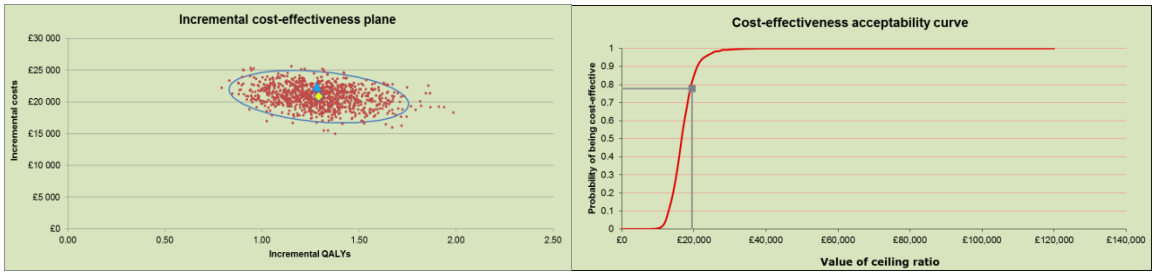
Figure 11 – PSA results for GT1 TN IE in Base Case model: SOF+PR (12 weeks) vs. PR (48 weeks) with SVR from Hadziyannis et al. 2004



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 34% and 80% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

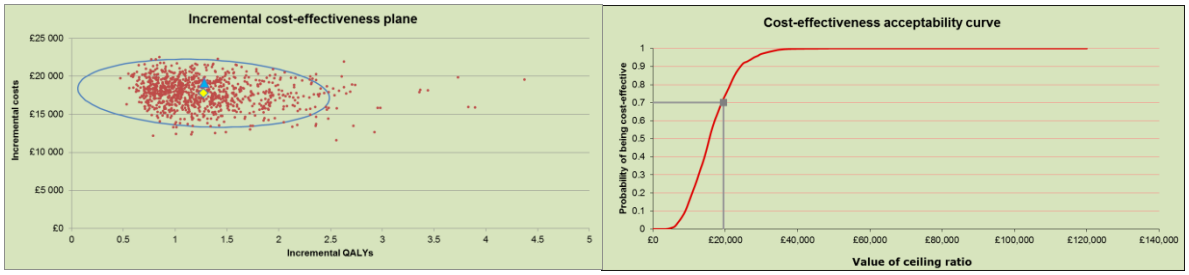
Figure 12 – PSA results for GT1 TN IE in Scenario analysis model: SOF+PR (12 weeks) vs. PR (48 weeks) with SVR from McHutchison et al. 2009



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 78% and 99% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

Figure 13 – PSA results for GT1 TN IE in Base case model: SOF+PR (12 weeks) vs. PR (48 weeks) with SVR from McHutchison et al. 2009

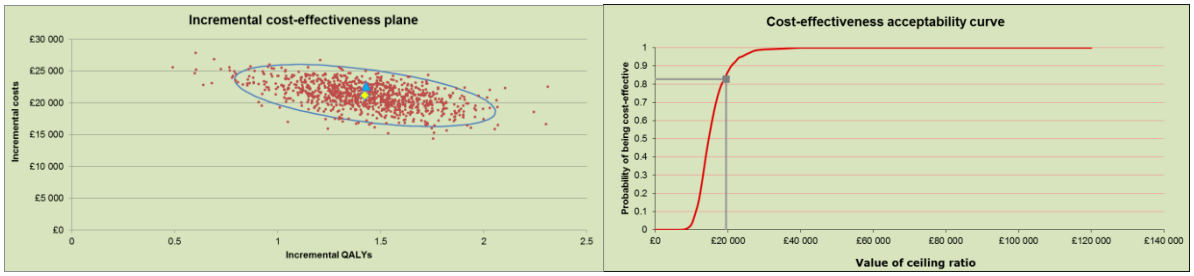


Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN IE patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 70% and 97% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

d. PSA results: HCV/HIV co-infected

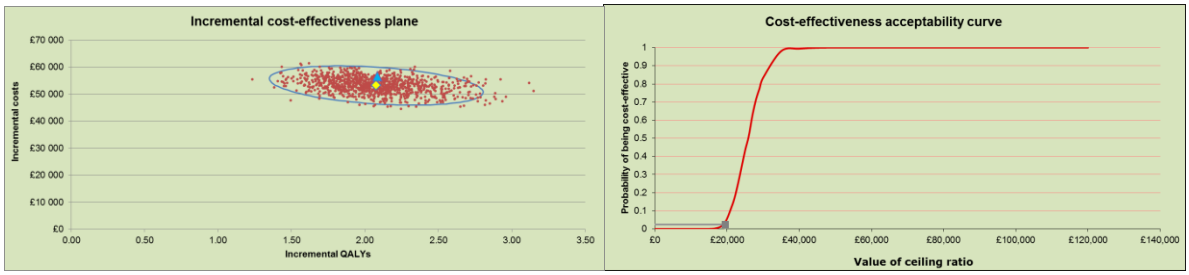
Figure 14 – PSA results for GT1 TN: SOF+PR (12 weeks) vs. PR (48 weeks)



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN HCV/HIV co-infected patients show that SOF+PR for 12 weeks has a probability of being cost-effective of approximately 83% and 99% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR.

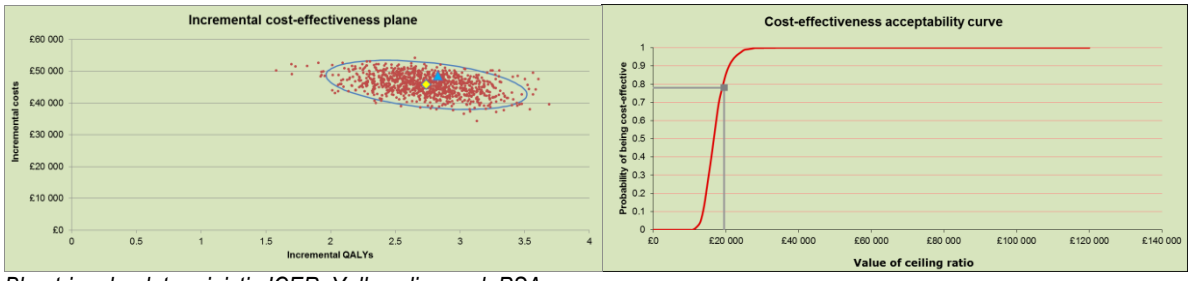
Figure 15 – PSA results for GT1 TN: SOF+RBV (24 weeks) vs. No treatment



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT1 TN HCV/HIV co-infected patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 2% and 83% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

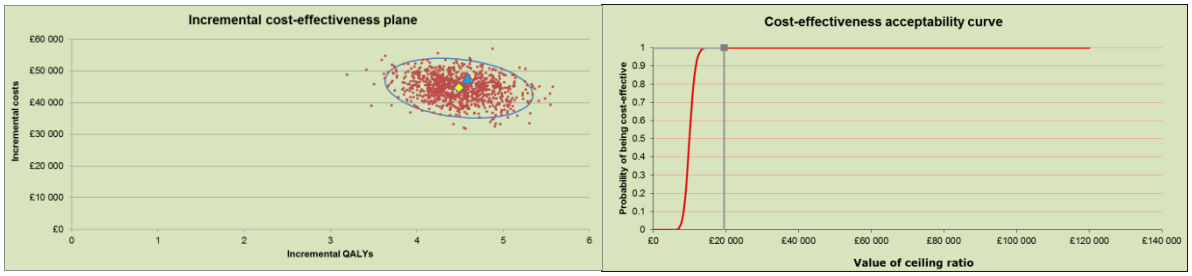
Figure 16 – PSA results for GT3 TE: SOF+RBV (24 weeks) vs. PR (48 weeks)



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TE HCV/HIV co-infected patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 80% and 100% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with PR for 48 weeks.

Figure 17 – PSA results for GT3 TE: SOF+RBV (24 weeks) vs. No treatment



Blue triangle: deterministic ICER; Yellow diamond: PSA average

The results from the PSA on GT3 TE HCV/HIV co-infected patients show that SOF+RBV for 24 weeks has a probability of being cost-effective of approximately 100% and 100% at a £20,000/QALY and £30,000/QALY threshold, respectively, compared with no treatment.

e. Probabilistic ICERs

Probabilistic ICERs for the scenario analyses conducted are presented in the tables below. These were calculated by estimating the 95% confidence ellipse. The difference between the deterministic ICER/QALY (referred in the tables as “Scenario”) and the probabilistic mean (referred in the tables as “PSA average”) is due to the variation of -10% given to all drug costs (since a uniform distribution was assigned to these parameters resulting in a wider spread of the simulations).

For the comparison of sofosbuvir against telaprevir (table 13) the 95% confidence intervals for the ICERs are relatively wide. This is due to the high uncertainty around the SVR rate for cirrhotic patients on telaprevir since the ADVANCE study only had a small number of cirrhotic patients (n=21). In our model we assigned a beta distribution to this parameter and

can observe that the SVR rates obtained from sampling this distribution vary considerably (95% CI: 41% to 81%).

6. Table 13 – Probabilistic ICERs for scenario 1 (appendix b)

Indication	Treatment strategies	Figure in answers to NICE	ICER (£/QALY) Scenario	PSA average	PSA lower bound	PSA upper bound
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	1	15,396	14,394	4,534	72,672
	SOF+PR vs. BOC+PR (RGT)	2	10,335	9,629	3,560	23,606
	SOF+PR vs. PR (48 wks)	3	17,476	16,110	10,528	27,154
GT1 TN UI	SOF+RBV vs. NT	4	47,611	45,159	28,842	91,655
GT3 TN IE	SOF+PR vs. PR (24 wks)	5	21,860	20,643	12,442	43,145
GT3 TN UI	SOF+RBV vs. NT	6	21,049	19,764	14,067	29,786
GT3 TE IE	SOF+PR vs. NT	7	9,006	8,340	4,556	15,757
	SOF+PR vs. PR (48 wks)	8	13,883	12,722	6,545	30,837
GT3 TE UI	SOF+RBV vs. NT	9	27,483	25,881	18,243	40,327

Table 14 – Probabilistic ICERs for scenario 2 (appendix c)

Model	SVRs Sources	Figure in answers to NICE	ICER (£/QALY) Scenario	PSA average	PSA lower bound	PSA upper bound
Scenario analysis model	Hadziyannis et al. 2004	10	25,014	23,603	15,019	44,280
Scenario analysis model	McHutchinson et al. 2009	12	17,476	16,110	10,528	27,154

Table 15 – Probabilistic ICERs for HCV/HIV co-infected scenario (appendix d)

Indication	Treatment strategies	Figure in answers to NICE	ICER (£/QALY) Scenario	PSA average	PSA lower bound	PSA upper bound
GT1 TN	SOF+PR vs. PR (data for SOF from trial 1910)	14	15,866	14,874	8,569	30,486
	SOF+RBV vs. NT	15	27,059	25,596	17,545	41,754
GT3 TE	SOF+RBV vs. PR (SVR for PR from Lagging+Shoeb)	16	17,167	16,679	11,587	25,351
	SOF+RBV vs. NT	17	10,376	9,933	7,165	13,652