Prevention of progression to cirrhosis in hepatitis C with fibrosis: Effectiveness and cost effectiveness of sequential therapy.

Rita Faria, Beth Woods, Susan Griffin, Stephen Palmer, Mark Sculpher

Centre for Health Economics, University of York

Stephen D Ryder

Nottingham Digestive Diseases Centre, University of Nottingham and Nottingham University Hospitals NHS Trust and Biomedical Research Unit.

15th March 2016

CHE
Centre For Health Economics

Funding

Financial support for this study was provided by the UK Department of Health Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The views expressed in this report are those of the authors and not those of the UK Department of Health. Any errors are the responsibility of the authors.

Outline

1. Background
2. Objectives
3. Methods
4. Results
5. Price tool
6. Limitations
7. Conclusions

1. Background (i)

- **214,000 individuals are chronically infected with hepatitis C (HCV) in the UK**
  - HCV virus presents different genotypes, which affect prognosis.
  - 90% of infections in the UK are by HCV genotypes 1 and 3.

- **Chronic hepatitis C has important consequences for health, public health and NHS costs**
  - Causes liver fibrosis, cirrhosis, end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC).
  - Half of injecting drug users tested positive for HCV infection.
  - Hospital admissions from HCV-related ESLD and HCC rose from 950 in 2004 to 2,658 in 2013.
  - 15% of all liver transplants were carried out in patients with hepatitis C-related disease.

CHE
Centre For Health Economics

1. Background (ii)

- **Treatment goals:**
  - Achieve sustained virologic response (SVR), widely regarded as cure
  - SVR halts disease progression at the pre-cirrhosis stages
  - SVR reduces the speed of disease progression at cirrhosis and decompensated cirrhosis
  - SVR increases quality of life

- **Standard treatment was peginterferon with ribavirin (PR) to up to 48 weeks** (in combination with protease inhibitors boceprevir and telaprevir in HCV genotype 1).
  - Long treatment duration.
  - Injectable treatment.
  - Adverse side effects, some long term.
  - Cure rates between 45%-80%, depending of patients' characteristics and HCV genotype.

1. Background (iii)

- **Emergence of the new direct-acting antivirals:**
  - Simeprevir (SMV), sofosbuvir (SOF), sofosbuvir-ledispavir (SOF+LED), daclatasvir (DCV), ombitasvir-paritaprevir-ritonavir with or without dasabuvir (2D/3D).
  - Higher cure rates and lower adverse events than PR.
  - Higher cost: >£25,000 per treatment course.
  - Assessed through the NICE single technology appraisal process.

- **NICE technology appraisals recommended new direct-acting antivirals as options in some subgroups:**
  - Simeprevir in HCV genotypes 1 and 4
  - Sofosbuvir-ledipasvir in HCV genotypes 1 and 4.
  - Sofosbuvir in some subgroups in HCV genotypes 1-6.
  - Daclatasvir in some subgroups in HCV genotypes 1, 3 and 4.
  - Ombitasvir-paritaprevir-ritonavir with or without dasabuvir in HCV genotypes 1 and 4.

CHE
Centre For Health Economics

1. Background (iv)

- **Challenges in implementing NICE guidance:**
  1. NICE cost-effectiveness assessments do not reflect treatment pathway
     - Assumed no retreatment of treatment failures.
     - Assumed that patients with decompensated cirrhosis are not treated.
     - Compare each new DAA with current standard of care and some of the new DAAs.
  2. NICE Guidance
     - Treatments recommended as options → lack of clarity in their positioning in the clinical pathway.
  3. Potentially large budget impact

When to treat? How to treat? How to retreat?

CHE
Centre For Health Economics

2. Objectives

- **What is the cost-effectiveness treatment strategy for patients with chronic hepatitis C at the METAVIR F3 stage?**
- Treatment strategies included:
  - Watchful waiting: no treatment at METAVIR F3 (advanced fibrosis pre-cirrhosis)
  - All the new direct-acting antivirals (DAAs) and pegylated interferon + ribavirin (PR) as single treatments or as two and three line treatment strategies at METAVIR F3
- All infected patients who progress to cirrhosis or decompensated cirrhosis are (re)treated with NHS England's commissioning policy

- **Not considered in the analysis:**
  - Management strategies for patients at the METAVIR F0-F2 stage

CHE
Centre For Health Economics

3. Methods

3.1 Population and subgroups

3.2 Treatment strategies

3.3 Modelling approach

3.4 Key data and assumptions

3.1 Population and subgroups

Advanced fibrosis (METAVIR F3)

HCV genotypes 1-4

Eligible for interferon		Ineligible for interferon
Treatment-naïve	Treatment-experienced	Treatment-naïve

CHE
Centre For Health Economics

3.2 Treatment strategies (i)

Treatments	HCV genotype			
	Genotype 1	Genotype 2	Genotype 3	Genotype 4
PR	48	24(48)	24(48)	48
SMV+PR	12+24 (12+48)			12+24 (12+48)
SOF+PR	12		12	12
SOF+RBV	24	12	24	24
SOF+LED	8 (12)			12
SOF+LED+RBV			12	
3D+/-RBV	12			
2D+RBV				12
SOF+DCV	12		12	12
DCV+PR				24+48

Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.

3.2 Treatment strategies (ii): The example of genotype 2

- No treatment at the F3 stage and treatment at F4
- PR over 24 weeks
- SOF+RBV over 12 weeks
- PR over 24 weeks then SOF+RBV over 12 weeks for those patients who did not achieve SVR
- SOF+RBV over 12 weeks then PR over 48 weeks for those patients who did not achieve SVR

Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin.

CHE
Centre For Health Economics

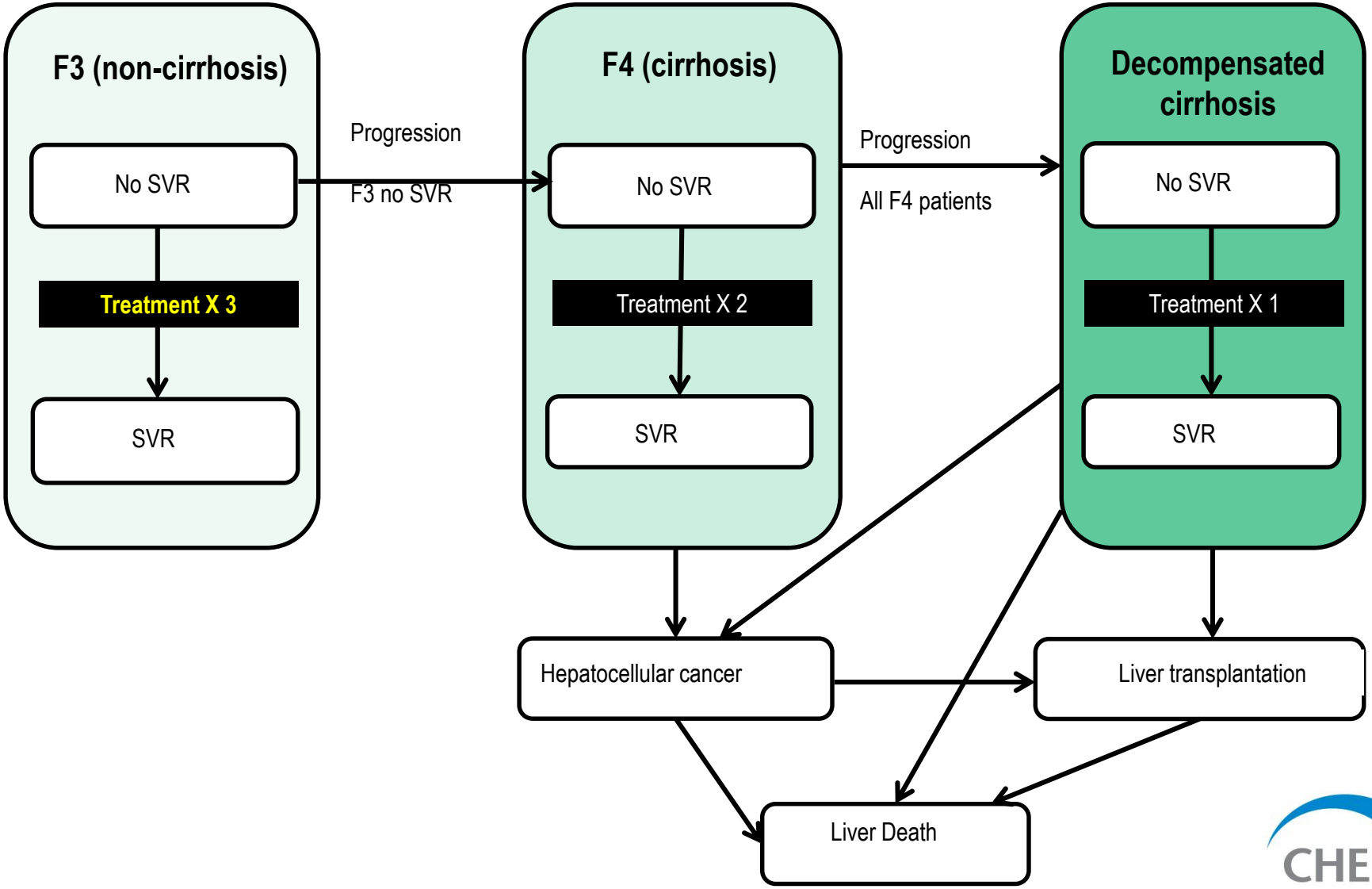
3.2 Treatment strategies (iii)

- All possible sequences of the new DAAs and PR as per product licenses:
  - SOF+LED over 12 weeks for G1 was excluded since more expensive and not more effective than SOF+LED over 8 weeks.
  - SOF+LED+RBV over 12 weeks instead of over 24 weeks as per BASL guidelines.
  - Watchful waiting at the METAVIR F3 stage: no treatment until progression to F4 (cirrhosis).

- Sequences constrained by:
  - PR based treatments can be used up to twice in the sequence.
  - Treatment combinations are not repeated; e.g. in the model, patients who fail SOF+LED are not given SOF+LED again.
  - PR alone cannot follow treatments which used PR with another drug.
  - 633 treatment strategies under comparison

Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.

3.3 Modelling approach



CHE
Centre For Health Economics

3.4. Key data and assumptions (i)

- The model evaluates different treatment strategies at the F3 stage.
- The model assumes that treatment at cirrhosis and decompensated cirrhosis:
  - Is immediate upon progression to health state.
  - Follows NHS England commissioning policy.
  - Cirrhotic patients who fail the first treatment are retreated once.
- Parameter inputs obtained from previous NICE TAs, supplemented by targeted searches.
- Drug costs are obtained from public list prices.

CHE
Centre For Health Economics

3.4. Key data and assumptions (ii): Probability of cure

Treatment	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Treatment-naïve interferon eligible				
PR	793/1772 (45%)	44/54 (81%)	99/139 (71%)	35/69 (51%)
SMV+PR	(80%)	-	-	27/32 (84%)
SOF+PR	220/240 (92%)	-	38/39 (97%)	33/33 (100%)
SOF+LED+/-RBV	202/215 (94%)	-	21/21 (100%)	387/396 (98%)
2D/3D+/-RBV	(97%)	-	-	42/42 (100%)
SOF+DCV	41/41 (100%)	-	73/75 (97%)	41/41 (100%)
SOF+RBV	-	88/91 (97%)	86/92 (93%)	-
DCV+PR	-	-	-	56/69 (81%)

Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.

3.4. Key data and assumptions (iii): Treatment prices

Treatment	Price per treatment course
PR	24 weeks= £4,904 48 weeks=£9,809
SMV+PR	12+24 weeks=£27,302 12+48 weeks=£32,207
SOF+PR	12 weeks=£37,435
SOF+LED	8 weeks=£25,987 12 weeks=£38,980 12 weeks + RBV=£39,944

Treatment	Price per treatment course
SOF+RBV	12 weeks=£35,947 24 weeks=£71,894
2D/3D+/-RBV	3D+/-RBV 12 weeks=£35,665 2D+RBV 12 weeks=33,164
SOF+DCV	12 weeks=£59,499
DCV+PR	24+48 weeks=£58,841

Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.

CHE
Centre For Health Economics

3.4. Key data and assumptions (iv): Value of information

Parameter	Value
Incident F3 population	1,163 patients per year
Proportion of treated incident patients	50%
Prevalent F3 population	16,819 patients
Proportion of treated prevalent patients	3% per year
Patients by HCV genotype	45% genotype 1 7% genotype 2 44% genotype 3 4% genotype 4
Patients by treatment status	26% treatment-experienced 14% ineligible or intolerant to interferon
Time horizon	10 years

CHE
Centre For Health Economics

RESULTS

CHE
Centre For Health Economics

Analysis and presentation of results

- Results fully probabilistic over 5,000 simulations
- 14 subgroups
- 633 treatment strategies
- Evaluated at threshold =£20,000/QALY (base-case)
- Range of outputs recorded.

- Only the cost-effective strategy at £20,000/QALY is shown.
- Full results available in forthcoming paper.

CHE
Centre For Health Economics

4. Results: base-case by subgroup

Sequence	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Interferon eligible treatment-naïve				
1st line	SOF+LED 8w	PR 24w	PR 24w	PR 48w
2nd line	3D+/-RBV	SOF+RBV	SOF+PR	2D+RBV
3rd line	SOF+PR	-	SOF+LED+RBV	SOF+LED
Interferon ineligible treatment-naïve				
1st line	SOF+LED 8w	SOF+RBV	SOF+LED+RBV	2D+RBV
2nd line	3D+/-RBV	-	SOF+DCV	SOF+LED
3rd line	SOF+DCV	-	SOF+RBV 24w	SOF+DCV
Treatment-experienced				
1st line	3D+/-RBV	SOF+RBV	SOF+PR	2D+RBV
2nd line	SOF+LED		SOF+LED+RBV	SOF+LED

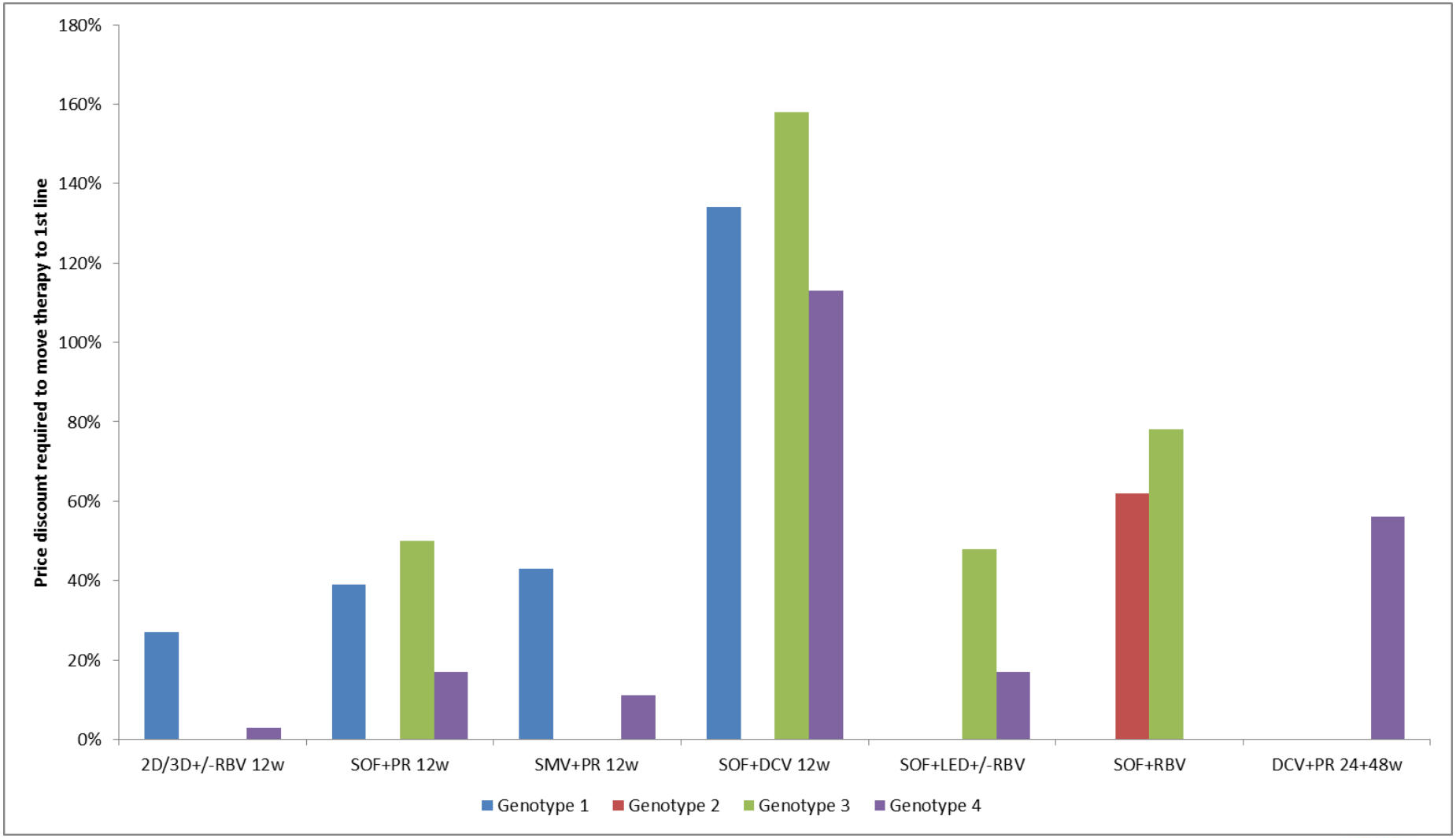
Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.

4. Results: sensitivity analysis

- 12 scenarios tested:
  - Slower speed of progression — 3rd line treatment changes in G3 III
  - Greater effect of achieving SVR on progression and quality of life
  - No treatment at cirrhosis and decompensated cirrhosis
  - Changed drug costs at cirrhosis and decompensated cirrhosis. — 3rd line treatment changes in G3 III/IE
  - Age at model entry.
  - Adherence to PR.

CHE
Centre For Health Economics

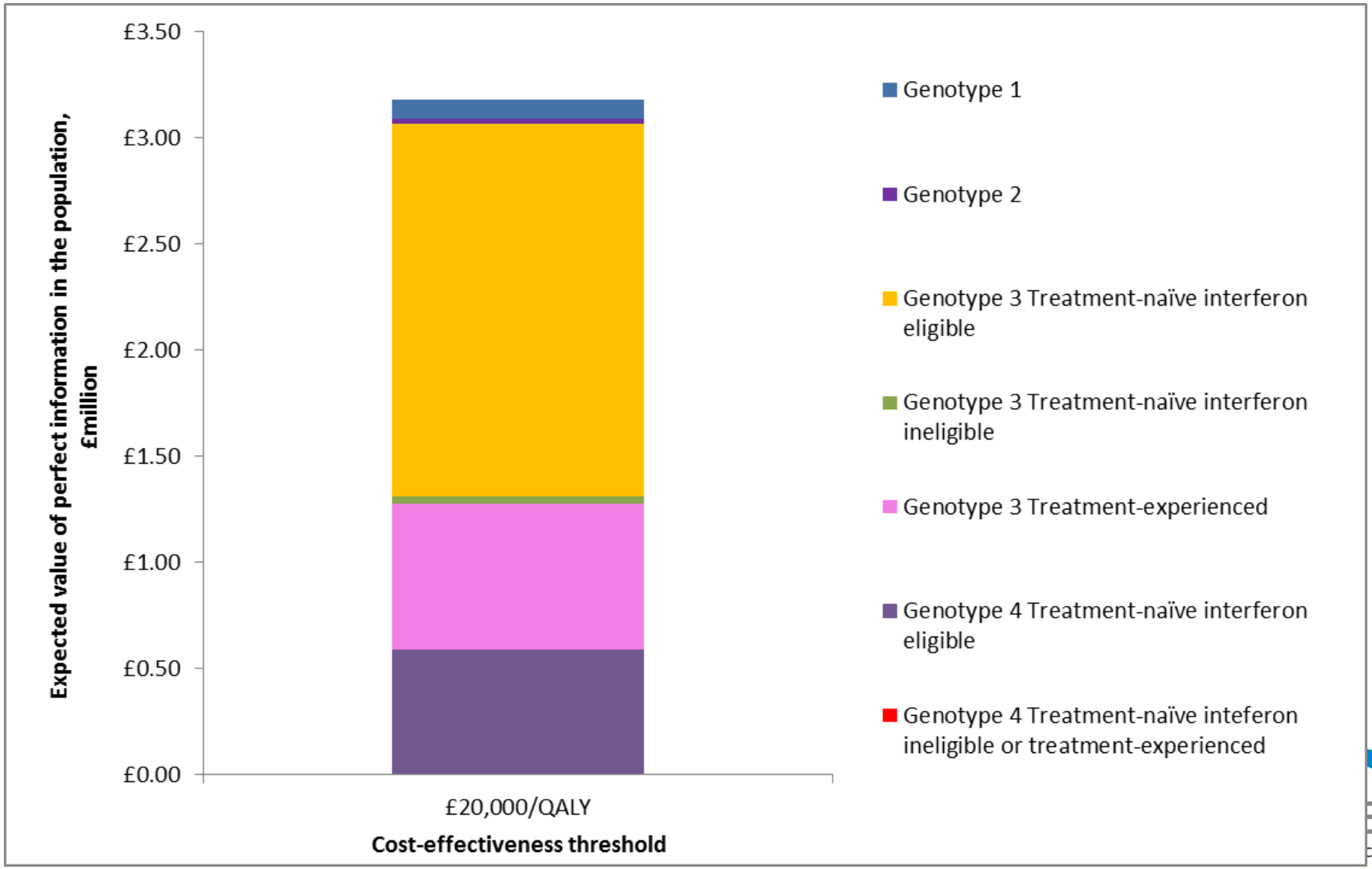
4. Results: threshold analysis on price

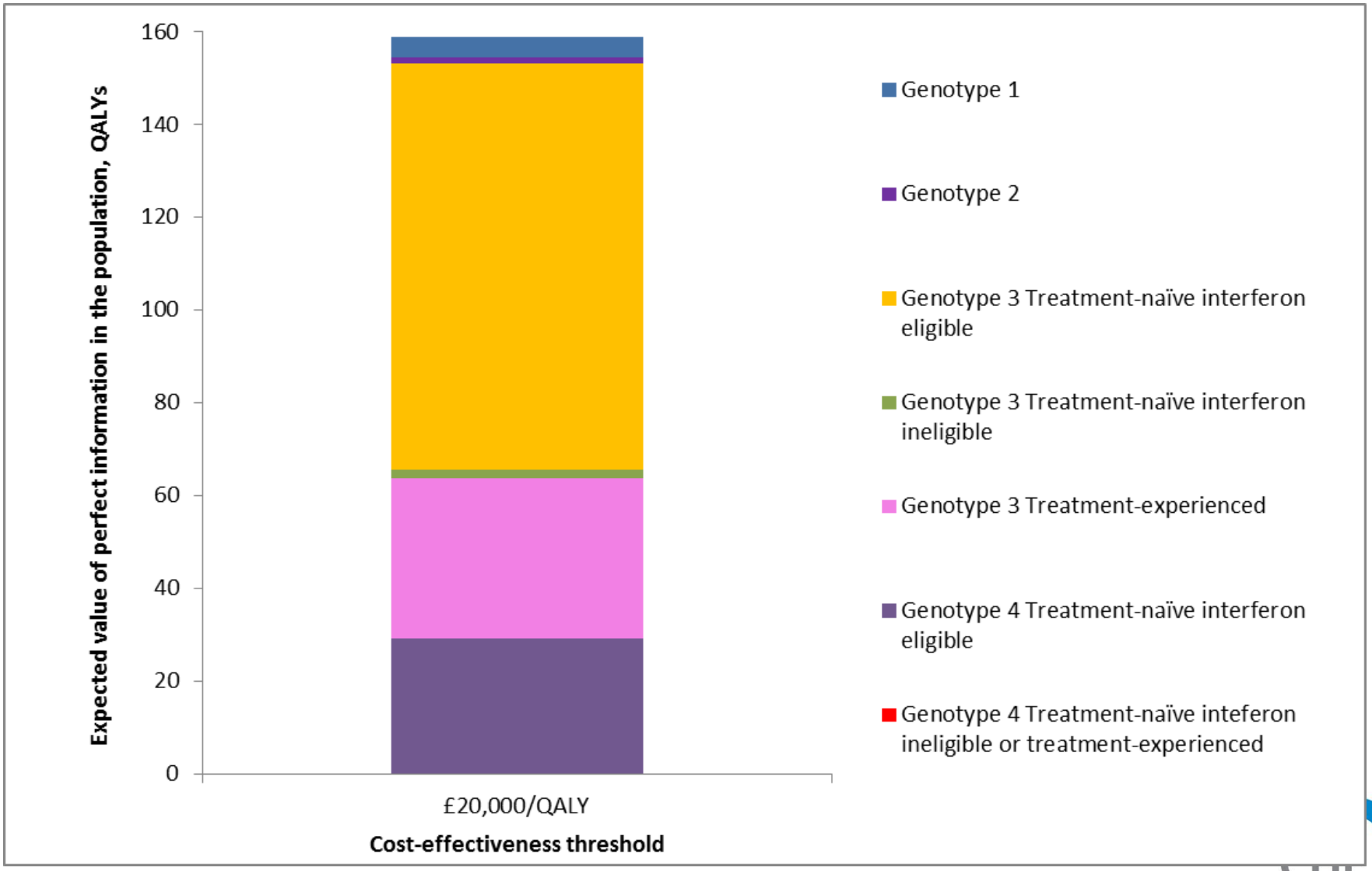


Treatments: SOF: sofosbuvir. LED: ledipasvir. RBV: ribavirin. PR: pegylated interferon with ribavirin. SMV: simeprevir. DCV: daclatasvir. 3D/2D: ombitasvir-paritaprevir-ritonavir with or without dasabuvir, with or without ribavirin.
Peginterferon not considered in the analysis given its relatively low price.

Centre For Health Economics

4. Results: value of information





Centre For Health Economics

5. Price tool

Price inputs

Generic name	Brand name	Packet size	New price	OR	Discount	UK list price
Sofosbuvir	Sovaldi	28				£11,661
Simeprevir	Olysio	7				£1,867
Pegylated interferon	Pegasys 180mcg	1				£124
Ribavirin	Copegus	168				£321
Ledipasvir-Sofosbuvir	Harvoni	28				£12,993
Ombitasvir-paritaprevir-ritonavir	Viekirax	56				£10,733
Dasabuvir	Exciera	56				£933
Daclatasvir	Daclinza	28				£8,173

This is the price used as default

Insert EITHER the new price OR the % discount in the green box

Cost-effectiveness threshold £20,000 Insert the relevant cost-effectiveness threshold; default is £20,000 per QALY gained

Calculate cost-effective strategies

Press this button for the model to calculate the cost-effective strategies

Results: Cost-effective strategy for each subgroup

Treatment-naïve patients

	Cost-effective strategies			% Patients achieving SVR by line			Treatment cost by line			Total	Total	ICER
Subgroup	1st line	2nd line	3rd line	1st	2nd	3rd	1st	2nd	3rd	Costs	QALYs	
Genotype 1 interferon ineligible	SOF+LED 8w	3D+/-RBV 12w	SOF+DCV 12w	92%	6%	0%	£25,918	£2,230	£145	£29,700	12.05	£10,867
Genotype 1 interferon eligible	SOF+LED 8w	3D+/-RBV 12w	SOF+PR 12w	92%	6%	0%	£25,918	£2,228	£90	£29,675	12.05	£5,106
Genotype 2 interferon ineligible	SOF+RBV 24w			91%	0%	0%	£35,341	£0	£0	£40,251	11.93	Lowest cost
Genotype 2 interferon eligible	PR 24w	SOF+RBV 24w		77%	17%	0%	£4,102	£6,731	£0	£14,475	11.92	Lowest cost
Genotype 3 interferon ineligible	SOF+LED+RBV 12w	SOF+DCV 12w	SOF+RBV 24w	92%	4%	0%	£39,355	£2,510	£238	£44,284	11.99	£12,189
Genotype 3 interferon eligible	PR 24w	SOF+PR 12w	SOF+LED+RBV 12w	66%	21%	5%	£4,099	£9,470	£2,202	£20,545	11.81	Lowest cost
Genotype 4 interferon ineligible	2D+RBV 12w	SOF+LED 12w	SOF+DCV 12w	95%	2%	0%	£32,548	£851	£72	£35,300	12.02	£9,486
Genotype 4 interferon eligible	PR 48w	2D+RBV 12w	SOF+LED 12w	46%	43%	1%	£6,431	£14,320	£323	£28,099	11.71	Lowest cost

PR: pegylated interferon with ribavirin. SMV+PR: simeprevir with pegylated interferon and ribavirin. SOF+PR: sofosbuvir with pegylated interferon with ribavirin. SOF+LED: sofosbuvir with ledipasvir.
SOF+LED+RBV: sofosbuvir with ledipasvir and ribavirin. 3D+/-RBV: ombitasvir with paritaprevir with ritonavir and dasabuvir with or without ribavirin.
2D+RBV: ombitasvir with paritaprevir with ritonavir and ribavirin. SOF+DCV: sofosbuvir with daclatasvir. DCV+PR: daclatasvir with pegylated interferon and ribavirin.

Treatment duration is indicated in weeks. For example, SOF+LED 8w refers to a treatment over 8 weeks.

Treatment-experienced patients

	Cost-effective strategies			% Patients achieving SVR by line			Treatment cost by line			Total	Total	ICER
Subgroup	1st line	2nd line	3rd line	1st	2nd	3rd	1st	2nd	3rd	Costs	QALYs	
Genotype 1 experienced to interferon	PR 48w	3D+/-RBV 12w	SOF+LED 12w	41%	47%	2%	£6,110	£17,068	£719	£31,011	11.72	Lowest cost
Genotype 1 experienced to protease inhibitors	SMV+PR 12+24w	3D+/-RBV 12w	SOF+LED 12w	76%	18%	1%	£25,929	£6,746	£284	£36,397	11.90	Lowest cost
Genotype 2 experienced to interferon	PR 24w	SOF+RBV 24w		77%	17%	0%	£4,102	£6,731	£0	£14,475	11.92	Lowest cost
Genotype 3 experienced to interferon	PR 24w	SOF+PR 12w	SOF+LED+RBV 12w	66%	21%	5%	£4,099	£9,470	£2,202	£20,545	11.81	Lowest cost
Genotype 4 experienced to interferon	PR 48w	2D+RBV 12w	SOF+LED 12w	46%	43%	1%	£6,431	£14,320	£323	£28,099	11.71	Lowest cost
Genotype 4 experienced to protease inhibitors	SMV+PR 12+24w	2D+RBV 12w	SOF+LED 12w	78%	16%	0%	£25,507	£5,468	£122	£34,441	11.90	Lowest cost

6. Limitations

- Focus on pre-cirrhotic patients (METAVIR F3), assumed diagnosed.
- Parameter inputs
  - Based on the NICE TAs.
  - No evidence synthesis.
  - Naïve comparisons between individual trial arms.
  - Generalisation between subgroups.
- Public list prices
- No reinfection or onward transmission → results not generalisable to transmitting population.
- Uncertainty in population size.

CHE
Centre For Health Economics

7. Conclusions

- It is cost-effective to treat at METAVIR F3
  - Patients should receive at least two lines of therapy
  - There is uncertainty about whether it is cost-effective to use a 3rd line of therapy in some subgroups
- PR still has a role to play at METAVIR F3.
  - Cost-effective as first line in HCV genotypes 2, 3 and 4.
  - Large price reductions are required for new DAAs to be cost-effective at first line in these genotypes.
- Our analysis provides clarity regarding which of treatments recommended by NICE should be used in practice
  - Example for genotype 1 1st line - NICE recommended: SMV+PR, SOF+PR, SOF+LED, 3D+/-RBV, SOF+DCV.
  - Our analysis suggests SOF+LED over 8 weeks.
- Value of additional research is concentrated in genotype 3 patients.

CHE
Centre For Health Economics

THANK YOU

CHE
Centre For Health Economics