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Hepatitis C

Understanding factors that influence the physicians' treatment decisions

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Preface

Disclaimer: This research was conducted and reported in 2013, when the most common treatment for Hepatitis C was a combination of ribavarin and interferon.

This report is intended to help improve understanding of the factors which influence the decisions of healthcare professionals to commence and continue treatment for Hepatitis C. The report focuses on four large Europeancountries: France, Italy, Spain and the UK. Comparison of decisionmaking in these countries has facilitated our understanding of common elements that influence clinician decisions and the contextual factors that differentiate the decisionmaking process. The methods used in this study include a literature review, key informant interviews, discrete choice experiment and the results of an expert workshop which informed scenario development.

The intended audience for this report is pharmaceutical companies, physicians and healthcare professions, policymakers and members of the public with an interest in treatment decisionmaking.

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Contents

Table of figures

Table of tables

Abbreviations

BMI	Body Mass Index
CSAPA	Centre de Soins Aux Personnalités Addictives
DOF	Degrees of Freedom
DCE	Discrete Choice Experiment
EASL	European Association for the Study of the Liver
EPO	Erythropoietin
EU	European Union
GP	General Practitioner
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU	Injecting Drug User
PEG IFN/RBV	Pegylated-Interferon and Ribavirin Combination Therapy
QALY	Quality-Adjusted Life Year
RCT	Randomised Clinical Trial
RNA	Ribonucleic Acid
SERT	Servizio per la Tossicodipendenze
SVR	Sustained Viral Response
TCP	Thrombocytopenia
UK	United Kingdom

Executive summary

Introduction

The Hepatitis C virus (HCV) is a blood-borne virus and a leading cause of chronic liver disease, end-stage cirrhosis, and liver cancer. Prevalence rates in Western Europe, according to the European Association for the Study of the Liver (EASL), are estimated at from 0.4% to 3% of the population, and it is estimated that the burden of HCV is likely to increase in Europe in the coming years. The clinical course of HCV differs; about 25% of patients resolve it without treatment over time, while the remaining 75% develop chronic infection.

The standard of care for chronic infection is peginterferon and ribavirin combination therapy (PEG-IFN/RBV), with treatment lasting from 24 to 72 weeks. While PEG-IFN/RBV reduces the risk of complications, such as cirrhosis, treatment initiation rates are low—about 10% of the diagnosed population—and discontinuation is an issue, mainly because of treatment side effects and the resistance of some forms of the disease to treatment. As a result, success rates vary between 40% and 80% depending on the patient disease genotype (from 1 to 6). Barriers to treatment include low platelet counts, because patients with HCV are at a higher risk of developing thrombocytopenia (TCP) given the side effects of HCV treatment and/or the biology of late stage liver disease. If platelet counts in patients with HCV and TCP can be increased, potentially treatment initiation, adherence to treatment and patient outcomes could improve.

While clinical trials provide accumulating evidence on treatment efficacy for different patient profiles and the clinical implications of treatment, we know very little about the physician treatment decision process and the factors that influence physicians' to initiate, continue, or stop treatment (i.e., how important low platelet count is in the physician decision to treat or not treat HCV patients).

This study's goal was to improve HCV treatment by (1) better understanding the nexus of factors physicians consider—e.g., clinical, social and behavioural, demographic, physician–experience-related, health and social care systems, regulatory, and policy—when making HCV treatment decisions; (2) investigating the comparative influence and importance of specific factors and combinations of factors and the trade-offs implicated in the decisionmaking process; and (3) examining how much TCP impacts treatment decisions and how it impacts treatment (e.g., its influence on decisions to begin or terminate treatment or adjust dosage and duration of treatment).

To meet this goal, we conducted five analyses, focusing on four European countries characterised by different approaches to healthcare organisation and financing, which alongside cultural differences may have potential implications for treatment pathways for patients with HCV infection. These were: France, Italy, Spain, and the United Kingdom. These analysis included:

1. Review the academic literature and of relevant national and European guidelines;
2. Conduct key informant interviews (KIIs) with national experts to contextualise the data from the literature review and further explore some emerging themes;
3. Map the patient journey in the four countries to identify stages HCV patients pass through once they have entered the healthcare system and map, for each stage, potential points of departure from the typical journey;
4. Design and conduct of Discrete Choice Experiments (DCEs) to quantitatively assess the importance of factors that influence treatment decisions;
5. Conduct expert workshop to help build scenarios identifying challenges to HCV treatment.

The five analyses build on one another, with the first three providing evidence that fed into the design of the DCEs and with the DCE results in turn serving as the key inputs into building the scenarios for the expert workshop.

Key Findings

The findings from each set of analyses are summarised below.

Literature Review Findings

Based on the literature review, two broad categories of factors have a role in influencing physicians' treatment decisions. The first relate to the **patient's profile** and include: (1) ***clinical factors***, such as viral genotype and haematological abnormalities (including TCP and anaemia); (2) ***comorbidities and related conditions***, such as HIV, Hepatitis B (HBV) and depression, side effects; (3) ***special population groups*** (including injecting drug users, alcohol-dependants, prison inmates, and migrants) and ***age-related groups***, including the elderly and children; (4) ***sociodemographic factors***, such as administrative region, income levels, and social inclusion; and (5) ***factors related to patient behaviour***, such as issues with adherence to treatment or substance misuse.

The second broad category of factors described in the literature relates to **health system features**, which include: (1) health financing and cost-effectiveness; (2) awareness and adherence to guidelines; and (3) access to care through eligibility criteria, collaboration between healthcare professionals and the wider health system stakeholders, and access to educational interventions to improve practice and alleviate fear and discrimination.

KII Findings

Although the literature defines the two broad categories of important factors in influencing physicians' treatment decisions, there was a lack of evidence on how physicians actually make decisions, and on the weight they attribute to the different factors in practice. Therefore, we conducted KIIs to elaborate on the information obtained from the

literature, give a country-specific perspective to that information, and start to understand the tradeoffs made when undertaking treatment decisions.

KIIs with five experts in HCV in the clinical and advocacy areas from each country—France, Italy, Spain, and the UK—highlight the **importance of the patient's profile in physician decisionmaking**. In general, the opinions of the experts were similar across the four countries. Genotype is a strong determinant for treatment in all four countries, and comorbidities (in particular, HIV, depression, diabetes, HBV and cirrhosis) influence decisions. Interviewees also highlighted the **role of demographic and behavioural factors in treatment decisionmaking, mainly in treatment initiation**, across all four countries. Most interviewees noted that the factors influencing the decision to treat special population groups are different from society at large because of complications surrounding adherence, the stigma of HCV, and different entry points and referral systems for these populations. For example, migrant status plays a role because of access to care and education barriers. When considering side effects, experts from all countries note that this involved tradeoffs depending on their level of severity.

Interviewees were also able to provide information about their country's **healthcare system and the impact of this on HCV treatment and decisions**. Interviewees report variation in the quality of care across and within counties, and under-diagnosis is viewed as a major problem, although diagnosis levels are increasing in some countries. However, interviewees also note that an increase in diagnosis would inevitably constrain resources and that the resource constraints would be exacerbated by the imminent arrival of new, more expensive therapies. Government support and funding appear to vary within countries, with, for example, large regional diversity in the UK and Spain.

Mapping the Patient Journey Findings

The mapping of the typical patient journey for each of the four countries under study partly drew on evidence extracted from the literature review and, more specifically, on the KIIs. This information was complemented by a targeted review of (national) policy documents and hospital guidelines for HCV and/or the treatment of HCV infection in the four countries. Drawing on this information enabled us to build a picture of the "typical" journey and to highlight the barriers and gaps patients encounter as they pass from diagnosis to treatment.

In general, **the referral process is two-phase**, with patients undergoing a preliminary diagnosis in primary care, often incidentally through a routine health check or by being treated for another ailment and then being referred to a specialist centre where the full diagnosis is given. Treatment is then provided in this specialist setting, such as a secondary care unit in a hospital or by outpatient specialist care, depending on the healthcare system, stage of disease, and clinical and behavioural characteristics.

There are some points of departure from this "typical" journey; they result mainly from general practitioners' (GPs') limited knowledge about HCV diagnostic tools and decisions, the capacity of the specialist providers to follow up with patients and offer continuity of care, the quality of care coordination and intra-professional collaboration across units, and the motivation and commitment of the individual patient.

DCE Findings

The findings from the literature review, KIIs, and path mapping highlighted a research gap where new empirical research could add value, i.e. the tradeoffs made by physicians in their decisions whether to treat different patients. These earlier stages of research also uncovered a range of possible factors that could be used as the basis of DCEs, from which the influence of each factor could then be quantified. DCEs provide a method for gaining *quantitative* insights into how different factors influence decisionmaking. Within a DCE, respondents are asked, in a survey context, to consider a range of hypothetical choice scenarios, each described by specific attributes, and indicate the decisions they would make in these scenarios. Respondents are forced to make tradeoffs and have to make pragmatic judgements about how they would respond in each situation, thus reflecting real-world decisionmaking.

In this case, 210 physicians—including gastroenterologists, hepatologists, infectious disease specialists, GPs, and specialist nurses—were surveyed across the four countries. There were two DCEs—one focused on the **factors influencing the decision to begin treatment**, and one focused on the **decision about if and when to make changes to the regimen of patients already being treated**; the two DCEs were presented in the context of a survey designed to also obtain information about the physicians themselves.

Physician Sample Findings. In our physician sample, a larger proportion of the individuals interviewed in Spain and France compared to the UK and Italy report that they make decisions on their own and are solely responsible for decisions in their unit, suggesting a greater degree of autonomy in these systems. Interestingly, these physicians were more likely to cease treatment than those without overall responsibility for a unit. In terms of physician perceptions of their healthcare systems, physicians generally feel positive about access to care, but opinions were mixed when specifically considering special populations—a particular issue in Spain and Italy.

Findings regarding the decision whether to commence treatment. Figure S.1 shows an example of the one of the scenarios (or vignettes) provided to physicians for the first DCE experiment, regarding the decision whether to commence treatment; each scenario contains a range of attributes that briefly characterise the patients' clinical history, their clinical and demographic characteristics, and their social characteristics. Each physician was asked to consider nine such vignettes and indicate for the patient in question whether they would decide to begin treatment.

Figure S.1: Example of a vignette for the first experiment, regarding the decision whether to commence treatment

The card below provides information about a hypothetical patient with a diagnosed case of Hepatitis C.
After reviewing their case given the information below, would you recommend this patient to initiate treatment?

Patient Information	
Gender	Male
Age	30
BMI	32 kg/m2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	Patient has no social-support network
Dependants	Patient has dependants who need support
Patient's motivation	Patient has reservations about treatment due to cultural/ethic background
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F3
Haemoglobin (anaemia)	8.5 - 10g/dl
Platelet count	80 000 – 100 000/mm3
White cells count/neutropenia	< 500/mm3
Co-morbidities	
Psychological disorders	Ongoing episodes of psychosis, currently under treatment
Other co-morbidities	Type-I Diabetes

◯ **Yes, I would recommend this patient to initiate treatment**

◯ **No, I would not recommend this patient to initiate treatment**

The findings from this first DCE experiment show that **a wide range of factors has a statistically significant influence on decisions to begin treatment:**

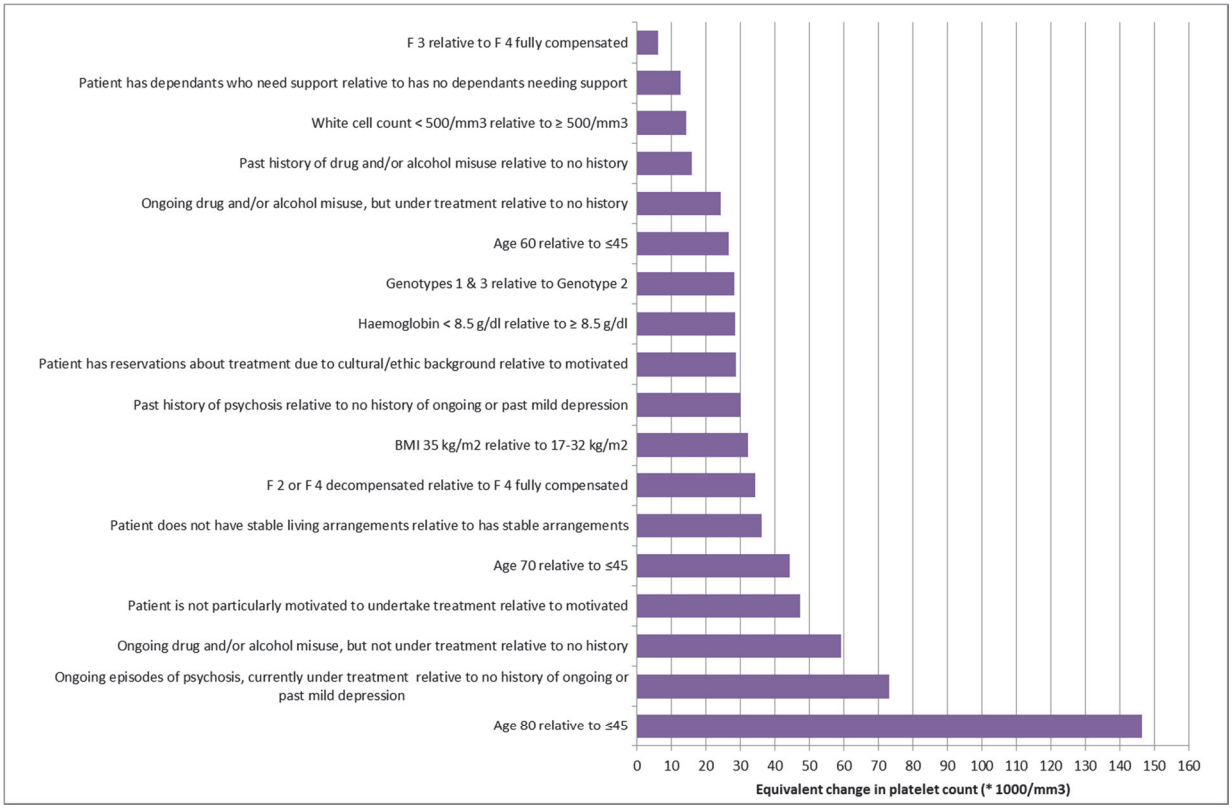
- Patient's age;
- Whether patients are severely obese;
- History of drug or alcohol misuse;
- Whether patients have stable living arrangements;
- Whether patients have dependants who require support;
- Level of motivation;
- Any history of psychosis;
- Clinical considerations, such as patients' genotype, the stage of the disease, and their haemoglobin, platelet, and white cell counts.

A number of patient factors were not found to have a statistically significant influence on the decision to treat; these include gender, social support network, and comorbidities.

The value added of DCEs and the modelling process that utilises the data is that we can quantify the relative weight placed on each factor in physicians' decisions to treat. For example, platelet count is identified as an important factor in influencing the decision to treat, and a number of studies focus on agents that can increase platelet counts in patients to ensure they are eligible for antiviral HCV therapy. In the KIIs, TCP is mentioned as an

important factor influencing decisions to initiate and continue treatment, in particular in Italy, Spain, and the UK. The DCEs provides further insight and allow us to quantify the relative importance placed on TCP compared to other patient characteristics in both the decisions about whether to initiate treatment and continue it. Figure S.2 shows the value of each of the factors found to be significant in the decision to treat, in units of equivalent change in platelet count.

Figure S.2 The value of patient attributes relative to a change in platelet count in physicians' decisions to treat patients

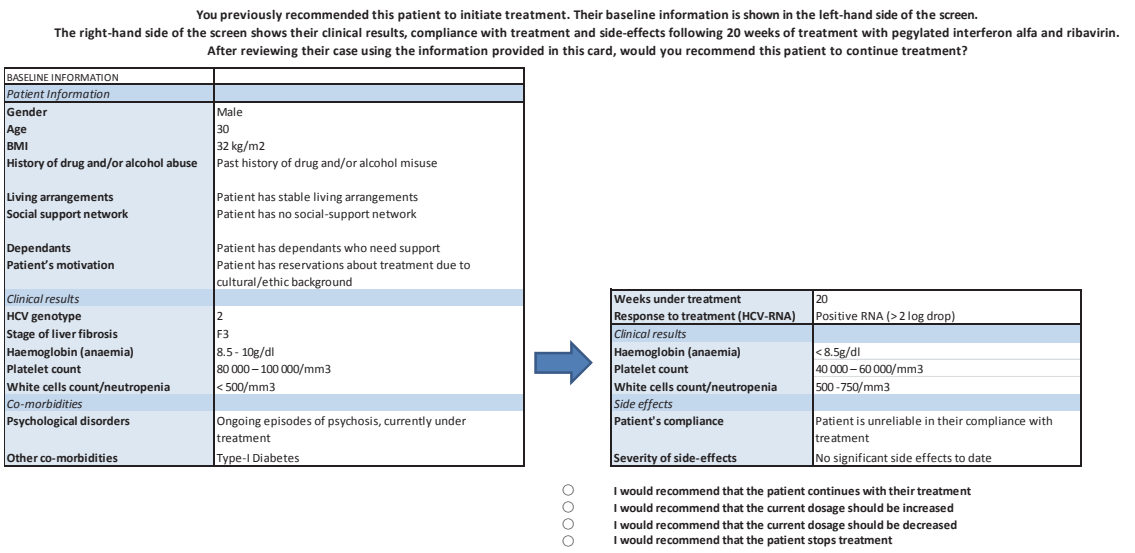


For example, if a physician has two patients who are identical in all other ways apart from one having a past history of drug or alcohol misuse, then the figure shows that that patient would need a platelet count that was *in excess of 14,000/mm^3 higher than the other patient to be considered for treatment over them*. The model from physicians choices also shows that a patient having an ongoing drug or alcohol misuse problem would require a platelet count i*n excess of 59,000/mm^3 higher than a patient without any history of misuse to be considered for treatment over them (all else being equal)*.

The relationship between platelet count and decision to treat is non-linear. The evidence from our study suggests that TCP leads to reductions in the likelihood of treatment, and that interventions that can increase platelet counts up to 70,000/mm^3 will act to increase the likelihood that any patient will be considered for initiation of treatment.

Findings regarding the decision whether to continue treatment. The second experiment concentrates on the factors influencing the decisions around continuing treatment, presenting the physicians with vignettes like the one shown in Figure S.3.

Figure S.3: Example of a vignette for the second experiment regarding the decision whether to continue treatment



You previously recommended this patient to initiate treatment. Their baseline information is shown in the left-hand side of the screen.
The right-hand side of the screen shows their clinical results, compliance with treatment and side-effects following 20 weeks of treatment with pegylated interferon alfa and ribavirin.
After reviewing their case using the information provided in this card, would you recommend this patient to continue treatment?

BASELINE INFORMATION	
Patient Information	
Gender	Male
Age	30
BMI	32 kg/m2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	Patient has no social-support network
Dependants	Patient has dependants who need support
Patient's motivation	Patient has reservations about treatment due to cultural/ethic background
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F3
Haemoglobin (anaemia)	8.5 - 10g/dl
Platelet count	80 000 – 100 000/mm3
White cells count/neutropenia	< 500/mm3
Co-morbidities	
Psychological disorders	Ongoing episodes of psychosis, currently under treatment
Other co-morbidities	Type-I Diabetes

Weeks under treatment	20
Response to treatment (HCV-RNA)	Positive RNA (> 2 log drop)
Clinical results	
Haemoglobin (anaemia)	< 8.5g/dl
Platelet count	40 000 – 60 000/mm3
White cells count/neutropenia	500 -750/mm3
Side effects	
Patient's compliance	Patient is unreliable in their compliance with treatment
Severity of side-effects	No significant side effects to date

○ **I would recommend that the patient continues with their treatment**
○ **I would recommend that the current dosage should be increased**
○ **I would recommend that the current dosage should be decreased**
○ **I would recommend that the patient stops treatment**

At this point, we find that **very few of the patients' background characteristics play a significant role in the decision to continue treatment**, with only their blood test results at treatment initiation (haemoglobin, platelet, and white blood cell counts) influencing the decision to continue, adjust, or terminate treatment. However, the patient's physiological response to treatment influences the decision whether to continue treatment, and patients are less likely to remain in treatment as time elapses, and if they do not have an appropriate RNA response. Deterioration in the levels of blood counts from baseline is a significant determinant in decreasing dose or ceasing treatment, but an increase in blood count levels from baseline does not increase the probability of continuing treatment. **Patient adherence to the treatment is another factor** observed to influence the decision. Those stated to be unreliable were more likely to have their treatment ceased. However, **side effects were not a significant factor** in the decision to decrease dose or cease treatment, perhaps because physicians use adherence as an indication of how much side effects can be tolerated.

Findings from applying the models

We have implemented these models of how factors influence physician decisions to begin and continue treatment into a forecasting system, which we use to calculate the likelihood of treatment in each of the countries for a patient with given characteristics. The forecasting system can examine the change in probability of treatment as different characteristics change, thus showing the influence of a given characteristic on the decision and presenting potential areas of future investigation to increase the number of patients undergoing successful treatment.

For example, for the patient shown in Figure S.4, we can explore the difference in probability of being accepted for treatment if he were instead experiencing severe TCP. Although the probabilities of being treated will vary according to the specific patient profile under consideration, we can show the influence that platelet count can have on the probability of treatment for an otherwise attractive patient and how this influence differs

between countries. This illustrates the power of DCEs in not only showing which factors are important in influencing treatment decisions, but also in *quantifying* the level of influence that each are likely to have based on the responses obtained from the structured choice experiments undertaken with a sizeable sample of physicians across the four countries of interest.

Figure S.4: Influence of variation in platelet count on probability of treatment for an example patient across four countries

Patient profile:

Patient Information	
Gender	*No impact on probabilities*
Age	60
BMI	17 - 32 kg/m2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	*No impact on probabilities*
Dependants	Patient has no dependants who need support
Patient's motivation	Patient is motivated to undertake treatment
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F4 fully compensated
Haemoglobin (anaemia)	8.5 - 10g/dl
Platelet count	> 60 000/mm3
White cells count/neutropenia	500 -750/mm3
Co-morbidities	
Psychological disorders	No history of psychological disorders, or current or past history of mild depression
Other co-morbidities	*No impact on probabilities*

Platelet count (/mm^3)	**Probability of treatment**			
	France	**Italy**	**Spain**	**UK**
>60,000	91%	72%	73%	87%
40-60,000	88%	64%	65%	82%
25-40,000	84%	57%	58%	77%
<25,000	79%	48%	49%	70%

Expert Workshop Findings

The results of the previous tasks were discussed in an expert workshop focusing on the current issues and how these might develop over time. Scenarios were developed around the common elements of context and uncertainty to illustrate the potential challenges and to examine shaping actions that could be taken to improve treatment prospects and patients' outcomes given the current clinical, policy, and innovation environments.

Workshop participants contributed to the development of the scenarios through systematically categorising the list of key factors influencing physicians' decisions, based on the perceived level of impact and the level of uncertainty of the factor. The scenarios were then focused on those factors that had a high impact and high level of certainty, and these were used to develop key shaping actions which could be adopted to support the development of each situation described. The scenarios were developed by RAND Europe around different models of care delivery: (1) ***community primary care***, targeted at hard to reach population groups; (2) ***care delivered in a network of specialist practices***; and (3) ***highly specialised centre-based care***. All these scenarios have different outcomes, advantages, and challenges. Depending on the scenario realised, there will be different impacts on the factors that are significant in treatment decisions today.

For example, in a community-based system, there will be less of an issue with living arrangements because the system will include local initiatives to help patients find suitable accommodation during treatment. Blood counts will no longer be a limitation in the

specialist care systems because close monitoring, along with specialist care and new medications to manage levels, will alleviate this. We would also anticipate that the influence of genotype on the decision to begin treatment will be reduced in specialised environments because of the presence of new medications and experienced physicians.

All scenarios could reduce the impact of psychological issues on treatment, through spillover improvements, close monitoring, or integrated care. Patient motivation could be improved in all scenarios by a variety of interventions, including the development of strong social networks at a community level, the promotion of one-to-one support by specialist nurses, and the introduction of new drugs with fewer side effects in specialised settings.

Such scenarios-based futures thinking can be used as a guide to inform ***shaping actions***—future strategic decisions that might be taken to either help situate oneself in any of the given scenarios and make plans or help take an active role in shaping different scenarios that might come to light in the future. Some examples of shaping actions addressing some of the relevant factors among clinical, lifestyle, and healthcare system-related characteristics include the following:

- Clinical: Current barriers to starting treatment and to deciding whether to continue treatment include levels of platelets and red and white blood cells. Thus, ***developing treatments that alleviate these issues would increase the number of patients who could commence and continue treatment.*** The issue of genotype could also be addressed if a new drug compatible with all forms of the disease were developed.

- Lifestyle: The main lifestyle factors identified as impacting the decision to initiate treatment were living arrangements, motivation, and a history of alcohol and substance misuse. Living arrangements were consistently highlighted as an issue, because of the current need to refrigerate medication. But such concerns may be alleviated with the move toward an oral pill rather than an injection. ***All these factors require coordinated interaction with other parts of the health and social care systems, and with the voluntary sector (e.g. patient associations)***. Support from psychiatrists throughout therapy could help patients with adherence issues, those with chaotic lifestyles, or those with current or previous alcohol or substance misuse.

- Healthcare system: There are major differences in physicians' propensity to treat across countries, and available resources and system organisation play a role in influencing these decisions. Interventions seeking to ***reshape elements of care standards and care delivery within healthcare systems*** are likely to optimise treatment rates. For example, identifying steps to facilitate the ***updating of guidelines to reflect best practice*** would constitute a system improvement. This can be complemented by ***implementing positive changes in the patient's journey in terms of flow and support***; doing so could increase adherence and also improve physicians' confidence in the system which, from our results, would in turn lead to an increase in treatment continuation.

Conclusions

Based on the results of this study we have identified key factors in physicians' decisions to treat Hepatitis C and have quantified the impact of TCP on treatment decisions. We have also looked at some of the policy implications of such factors in treatment decisions through scenario analysis. Below we summarise our key findings.

Factors Important in Influencing Physicians' Decisions to treat Hepatitis C

We used a multi-method approach to identify a number of factors important in affecting physicians' decisions to initiate HCV treatment for patients. As shown in Table S1, DCEs provide a valuable empirical way of confirming factors identified in the literature review and KIIs as important (e.g., age, country, genotype, history of alcohol/substance abuse), but DCEs were also useful in showing that factors important in the literature review and/or KIIs (e.g., comorbidities and gender) are not important to physicians and that factors not shown as important (or as important) in the literature review and KIIs (e.g., BMI, living arrangement, stage of disease) are more important to physicians.

Table S.1: Importance of factors in influencing physicians' decisions to treat

Factors	Literature Review	KIIs	DCEs
Age			
BMI			
Comorbidities			
Country			
Dependents			
Family support			
Gender			
Genotype			
Haemoglobin levels			
History of alcohol/substance misuse			
Living arrangements			
Patient motivation			
Platelet count			
Psychological disorders			
Stage of disease			
White blood cell levels			

* Key: Dark – high impact, Light – low impact, Clear – insignificant impact[1]

Interestingly, the factors involved in continuing treatment often differed from those influencing treatment initiation. At the continuation stage, for patients that had already been accepted for treatment, the patient's profile and circumstances were no longer

[1]Please note that those categories correspond to a qualitative assessment rather than quantitative measure of importance and significance, except for the DCE where the assessment is based on the quantitative findings.

important factors, and the decision focused on the clinical response to treatment. For example, significant factors include the duration of the treatment so far, the patient's adherence to therapy, and a reduction in haemoglobin, white blood cell, and platelet counts. However, although severe side effects were mentioned in the KIIs as a factor influencing the decision to continue treatment, this was not reflected in the DCE results.

Focus on the Impact of TCP on Treatment Decisions

Platelet count was identified as an important factor in influencing the decision to treat, and a number of studies in the literature review focus on agents that can increase platelet counts in patients to ensure they are eligible for antiviral HCV therapy. In the KIIs, TCP was mentioned as an important haematological factor influencing treatment decisions to initiate and continue treatment in Italy, Spain, and the UK. Interviewees in both Italy and the UK mentioned issues with the guidelines around the treatment of patients with low platelet counts, stating that the threshold levels were too high compared to reality. The views on the importance of TCP did vary across countries, with French interviewees stating that it was rare to interrupt treatment based on TCP.

The models estimated from the data collected through the DCEs provide further insight and allow us to quantify the relative importance placed on TCP alongside other patient characteristics in both the decisions about whether to initiate treatment and whether to continue treatment should TCP occur during treatment. One can examine a range of different patient profiles and, for each, to look at the difference that having, or not having, TCP will have on the patient's probability of receiving treatment. This can be used to illustrate the possible impact that may be achieved with new therapies that could reduce the onset of TCP.

Relative importance of factors and policy implications

While the DCEs illustrate the influence that each factor has on treatment decisions independent of each other, some of these factors are interrelated in actual patients, and a change in one factor may also lead to a change in another. Thus, in interpreting the findings, it is important to take this into account if considering how interventions may seek to influence these factors to improve the probability that certain patient groups will be judged as eligible or appropriate for treatment.

To validate the relationship between factors and assess their future impact on treatment decision, we explored the emerging findings with a workshop of experts and developed a set of scenarios. In the scenario building, blood counts, genotype, patient commitment (motivation at initiation, adherence at continuation), living arrangements, severe psychological issues, and collaboration within the healthcare system were considered as factors that may have a high impact on treatment decision, but whose impact could be decreased by appropriate interventions, including investment into new drug development, public health education campaign, etc.

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CHAPTER 1 Introduction

1.1 Background and context

Hepatitis C is a blood-borne virus and a leading cause of chronic liver disease, end-stage cirrhosis and liver cancer. An estimated 75% to 85% of infections progress to become chronic (Mukherjee and Dhawan, 2009). The true prevalence of chronic Hepatitis C Virus (HCV) infection is difficult to ascertain because of the slow progression and lack of specific symptoms at early stages. For example, recent estimations from the UK suggest that about 86% of those infected with HCV are unaware of their infection (European Medicines Group, 2007). The European Association for the Study of the Liver (EASL) estimates that the number of people with chronic HCV infection may well exceed 200 million world-wide, and in Western Europe the prevalence ranges from 0.4% to 3% of the population. HCV has become the major cause of liver cancers in Europe (EASL, 2011). As a blood-borne infection, HCV is most common in injection drug users (present and past), recipients of unsafe blood transfusion or blood products (in the past), and migrants from countries where HCV is endemic. These routes to transmission account for approximately 70% of infections in developed countries, although transfusion-related transmission has nearly been eradicated in Europe as a result of the routine screening of blood and blood products (EASL, 2011). There is a diversity of responses to the infection by patients – some seem to resolve it without treatment over time (between 15% and 25%), while others develop chronic infection (between 75% and 85%). Among those chronically infected, liver cirrhosis occurs in 10–30% of the cases, and every year between 1% and 3% develop hepatocellular carcinoma (HCC) (Rosen, 2011).

The well-accepted standard of care treatment is peginterferon and ribavirin combination therapy – PEG IFN/RBV (EASL, 2011). PEG IFN/RBV can help reduce the risk of developing more severe complications, such as cirrhosis, but treatment rates are low (c. 10% for diagnosed population) (Sarrazin et al., 2010). The primary goal of antiviral treatment of chronic HCV is the attainment of a sustained viral response (SVR), defined as undetectable serum HCV-Ribose Nucleic Acid levels six months after treatment cessation (Yang and Chung, 2011). Borroni et al. (2008) found 54–63% of clinical trial patients who have not received previous treatment (treatment-naive patients) to attain a SVR.

GlaxoSmithKline (GSK) has a thrombopoietin receptor agonist drug (Revolade) on the market. Revolade acts to increase the number of platelets in the blood. It is already being used to treat bleeding disorders in adult patients who have had their spleen removed and who did not respond to corticosteroid or immunoglobulin therapy. In recent clinical trials, Revolade has also shown promise in a new indication: for treatment of low platelet count

as one of the core complications to the effective treatment of HCV. Patients with HCV are at a higher risk of developing thrombocytopenia (low platelet count), because of the side-effects of HCV treatment and/or the biology of late stage liver disease. Low platelet counts can hinder HCV treatment in three ways: influencing the decision to initiate treatment by physicians, the prescribing of optimal dosages and the ultimate efficacy of the treatment. If platelet counts can be increased in patients with HCV, it is plausible that prospects for HCV treatment with the accepted standard treatment (combinations of interferon and ribavarin) and the outcomes of treatments for patients could improve.

Study objectives

GSK commissioned RAND Europe to conduct a study which aims to:

- better understand the nexus of factors physicians consider when making HCV treatment decisions for patients (e.g. clinical, social and behavioural, demographic, physician experience-related, health and social care systems, regulatory and policy),
- investigate the comparative influence and importance of specific factors and combinations of factors, and the trade-offs implicated in the decisionmaking process
- examine to what extent thrombocytopenia (TCP) specifically impacts on treatment decisions and how (e.g. influence on decisions to begin or terminate treatment or adjust dosage and duration of treatment).

In order to understand how patient outcomes can be improved, it is important to try to better understand the nexus of factors physicians consider when making decisions about HCV treatment, and to investigate the comparative influence and importance of specific factors and combinations of factors, and the trade-offs implicated in the decisionmaking process (e.g. influence on decisions to begin or terminate treatment or adjust dosage and duration of treatment). However, the evidence base behind treatment decisions for HCV is limited. A number of factors are thought to influence the decisions physicians make, but their relative impact remains elusive and there may be additional drivers of decisionmaking not captured in the current knowledge pool.

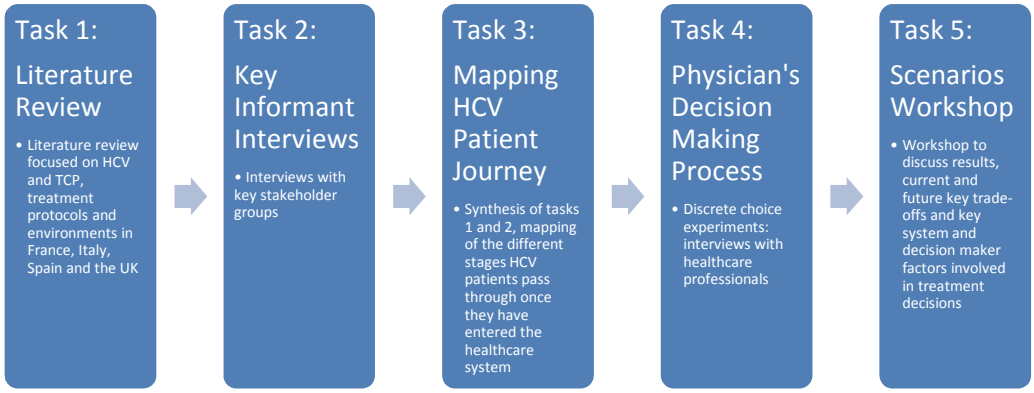
CHAPTER 2

Our methodological approach

2.1 Overview

RAND Europe carried out a set of interrelated tasks to understand the drivers of treatment decisions for patients with HCV and the influence of TCP. Figure 2.1 presents an overview of the approach.

Figure 2.1 Tasks to understand drivers for treatment decisions for HCV



The combination of tasks is designed to draw from a diverse evidence base including: "formal knowledge" published in journals; insights from patient groups, experienced practitioners and policymakers, which have not necessarily been written down or "codified"; and quantitative data collected from discrete choice experiments that will provide insights into the balance of trade-offs that clinicians make in their decisionmaking.

The approach focuses on both individual and system behaviour. We aimed to capture the impact of different behaviours and cultural factors that influence individuals in their approach to different treatment regimens, and the impact of diversity in the way health systems operate on treatment regimens and protocols.

The interviews and literature review provide background and context for the study, and inform the design of the stated preference discrete choice experiments. The results and implications of the stated preference experiments were discussed in the scenario development workshop.

We conducted the study in four large European countries: the UK, France, Italy and Spain. Comparison of decisionmaking in these countries will facilitate our understanding of common elements that influence clinician decisions and the contextual factors that differentiate the decisionmaking process. These countries are characterised by different

approaches to healthcare organisation and financing, which alongside cultural differences may have potential implications for treatment pathways for patients with HCV infection.

2.2 Literature review

The literature review aimed at identifying drivers that influence physicians' decisions to start, continue, adjust or stop HCV treatment across European (EU) contexts (France, Germany, Italy, Spain and the UK). A search protocol was designed around categories of search terms. This included an initial pilot, followed by an adapted approach.

2.2.1 Approach

Stage 1

The search term categories were the following:

- country names
- disease (Hepatitis C)
- treatment
- user profile factors (including the following sub-categories: related conditions and non-medical characteristics)
- health systems factors (including the following sub-categories: finance, regulation and organisation)
- decisionmaking-related factors (including the sub-categories: care regime and actions).

The full list of search terms is available in Appendix A. The search was limited to five languages: English, French, German, Italian and Spanish, and covered research undertaken between 2001 and 2012 and published in Embase or Pubmed.

An initial pilot search was undertaken to evaluate the amount of literature available, requiring that all the sub-categories were in the title or the abstract. This search was too restrictive, providing a total of 238 articles.

Stage 2

The search was adapted so that only one word from each category (and not one from each sub-category) was in the abstract or the title. Searching Embase and Pubmed (Search 1bis) retrieved 1,228 results. The search was then limited to articles and reviews, to focus on the strongest type of evidence.[2] This reduced the number of articles to 902. A scan by the research team allowed the exclusion of articles that focused uniquely on countries outside the scope, and not relevant to the study. This resulted in 776 articles. These articles were then matched with the initial set of 238, and duplicates were deleted, leaving a total of 896 articles. The title and abstracts of these articles were reviewed to reach a target of a selection of 100 documents. Criteria of selection were the relevance, quality and scope of

[2] For instance, commentaries and essays were excluded at this stage.

the study.[3] The research team also took into account the balance of countries, user (patient) profile factors (clinical, behavioural or socio-demographic) and health system factors (related to the provider experience and skills or to the wider system, including guidelines and pathways). The selection was discussed based on a triangulation process of our review team.

Stage 3

In the process of reviewing these articles, the researchers found that some articles focusing on the drug relevant to the client (eltrombopag, Revolade or both), and the condition that it treats (TCP) could have been omitted as a result of the restrictions built in the search process. A second search process was therefore designed to retrieve relevant articles (Search 2), where there were no country limitations, and the categories were Hepatitis C AND TCP AND (eltrombopag OR Revolade). This yielded 51 results. A selection was performed following the same rules as for Search 1 and 1bis, based on the relevance, quality and scope criteria.

Stage 4

The remaining articles along with a selection of guidelines[4] from the different countries, and articles and documents provided by the client, were then recorded on an abstract map, which reflected a total of 104 articles and guidelines. Each document addressed a core question about the nature of decisionmaking, such as the nature of the decision drivers and the stages of the decision process.[5] A final selection was made for articles to include in a full text review based on researcher ratings of relevance, balance of factors, and a subsequent validation scan of full text quality. This led to a selection of 22 articles for full text review. These 22 documents have been scored according to quality criteria (method strength, quality of the results, evidence robustness, among others) and analysed extensively. The full review summarises the key elements of each document, which include:

- the method
- key findings on factors influencing treatment decisions (e.g. their diversity, user profile related, health systems related)
- key findings on trade-offs and evidence of comparative weight of different factors and drivers, including at different stages of decisionmaking (begin, continue or adjust dosage, terminate)
- geographical coverage

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[3] Relevance: some articles retrieved were focusing solely on hepatitis B or HIV, for instance, with a simple mention of HCV in the abstract; quality: articles published in non-identifiable journals, or articles with an abstract that was poorly written, may have been excluded; scope: if the article focused solely on a specific country out of our scope, and the same topic was explored in a similar study within our scope, we may have excluded it. It includes for example Taiwan or Hong Kong articles which were less relevant to the review than US articles.

[4] These were identified through specific searches on the internet.

[5] It is important to note that in the abstract map (given the constraints of the budget and need to prioritise and focus in this task) some of the text is copy-pasted from abstracts and hence the abstract map is not for external dissemination outside GSK and RAND/Baird's.

- key findings on relevant commonalities and differences across geographical contexts (e.g. in drivers and their impacts on treatment decisions
- other relevant findings
- previous evidence (studies or publications and their findings) on which the paper drew to support its arguments
- new evidence being presented or raised in the discussion and critique.

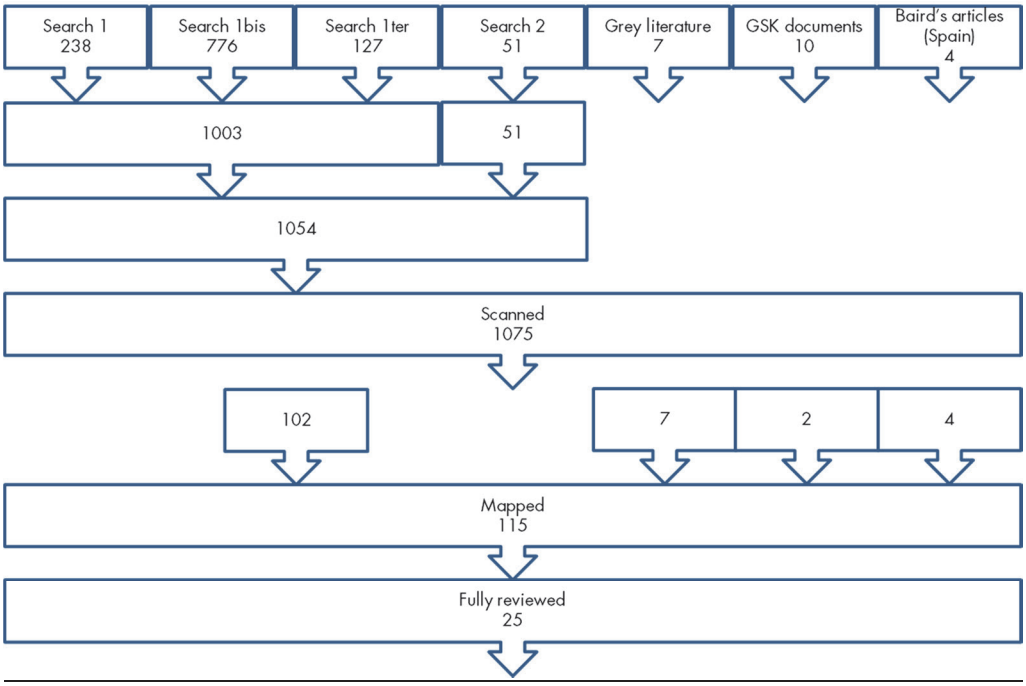
Stage 5

At the request of GSK, Spain was added as a country of interest later on in the research process. In order to be consistent with the previously described method, Search 1bis was conducted again, restricting the country limitations to Spain. The search (Search 1ter) gave 127 results, from which we removed duplicates by comparing results to previous searches. The full list was then reviewed through titles and abstracts following the above mentioned selection criteria. We retained five articles for abstract mapping and two for full review. The Spain search was complemented by the review of guidelines and several recently published articles recommended by Baird's CMC. This added a total of six more abstracts and one full review.

The final results of this design produced an abstract map of 115 articles and guidelines, with (to the extent that it is available) summary insight on decisionmaking processes and drivers, and a literature review drawing on insights from the 115 abstracts and 25 full text reviews.

Figure 2.2 summarises the number of articles retrieved and selected at each step.

Figure 2.2 Overview of literature search and selection



2.2.2 Caveats

There are a number of caveats to bear in mind regarding the literature review. First, we could not cover all the literature in the field but prioritised according to the criteria described in Section 2.2. This meant, for example, that the wider and more general health systems organisation issues (e.g. centralisation and decentralisation; public and private care) which relate across disease areas were not reviewed, but the influence of these factors was examined in other data gathering such as through interviews (Chapter 4). We also – given the scope of the task – drew information for the majority of studies from published abstracts, focusing on the core messages but not necessarily the nuances of the detailed study as these tend not to be described in abstracts. However, we did review the text of 25 prioritised articles in full.

The literature review will be complemented with primary research through key informant interviews and discrete choice stated preference experiments; this, together with the expert workshop, will ensure appropriate triangulation to ensure valid inference making from the wider project. In addition to methodological triangulation we have triangulated across researchers, by involving multiple researchers in the literature selection and the relevance and quality analysis of selected abstracts and articles.

2.3 Key informant interviews

Interviews were conducted with experts in the field of HCV and TCP treatment in France, Italy, Spain and the UK. Key informants were identified through a range of sources, including documented track record in the relevant scientific literature and/or international reputation through, for example, contribution to advisory groups. Further sources included suggestions from GSK, and senior advisors to the project. The final list of interviewees to approach was decided by the RAND Europe team without bias or influence from GSK.

Key informant interviews were carried out following standard methodological procedures and involved semi-structured interviews following a common interview guide, which was developed in consultation with the client. The interview guide can be found in Appendix B. The interviews were conducted by researchers whose first language was that of the interviewee, and one researcher carried out all of the interviews for a particular country. Interviews were carried out by telephone, and lasted between 45 minutes and an hour. The interviews were recorded and transcribed for analysis. They followed ethical principles of conducting research involving human subjects, only approaching key informants in their professional function and not collecting sensitive personal information. Data protection measures were put in place to maintain confidentiality of interview participants.

Data from the key informant interviews was coded manually and stored in a spread sheet format. This doesn't show which stakeholder group they relate to as identification of stakeholder groups could be a risk to anonymity. UK interviewees are coded 1–5; Italian 6–10; French 11–15, Spain 16–20.

There were 20 interviews conducted in total. The sampling frame was designed to ensure a range of stakeholders were interviewed. We were successful in obtaining a mix of professional profiles; and in some countries we were also able to interview experts working in different regions of the countries, so we could capture elements of regional context and compare them with other interviews to draw a more accurate national picture. Further information about the profile of the interviewees can be found in Appendix C.

2.3.1 Caveats and points for attention

The interviews provide a rich source of information, in addition to that collected through the literature review. However, we are aware of certain caveats and would like to draw attention to the following points:

- Despite efforts to standardise the interview process, not every interviewee answered in the same level of detail on every issue. Interviewees spoke based on their experience, and therefore there were different levels of breadth and depth in answers across interviewees.
- Some of the evidence is relatively subjective, so this needs to be taken into account when drawing inferences.
- The Italian respondents provided less detailed data than respondents from other countries.
- Interviewees spoke about many diverse factors influencing treatment decisions, and we attempted to ascertain the importance of these. The most important factors then fed into the choice modelling exercise, and these were judged on the basis of criteria such as how common a factor is across countries, the emphasis of factors in the interviews, or the level of uncertainty there is on how a factor influences a decision.

2.4 Mapping the patient journey

The mapping of the typical patient journey for each of the four countries under study drew, in part, on evidence extracted from the literature (Chapter 3) and, more specifically,

the interviews with key informants (Chapter 4). This information was complemented by a targeted review of (national) policy documents and hospital guidelines for HCV and/or the treatment of HCV infection in the four countries which were the focus of this study. This additional search retrieved 12 documents of which six provided additional insights into the patient journey. Documents included, for example, treatment guidelines issued by selected hospitals in the UK.[6] Drawing on this information enabled us to build a picture of the "typical" journey; this also sought to highlight the barriers and gaps patients encounter as they pass from diagnosis to treatment.

2.4.1 Caveats

There are certain caveats which we would emphasise. It is important to note that the information collected to inform the mapping of patient journeys was not always comprehensive, and as it draws on key informant interviews in particular may reflect personal and local experience rather than a more general vision about the efficiency of the healthcare system. Also, the patient journey is not standardised across countries or within countries. While all countries under study have issued guidelines on the treatment of HCV infection, there are generally no national guidelines describing the optimal care pathway from diagnosis to post-treatment follow-up.

2.5 Discrete choice experiments

The previous tasks were used to provide an overview of the current evidence base, and multiple-stakeholder views on factors that influence HCV treatment decisions. Through a process of internal workshops with those involved in the experimental design, literature review and interviews we identified a range of factors that are likely to influence physicians' treatment options and behaviours; these were further verified and refined through discussion with the project partners and our expert advisor. However, the question remained regarding the extent to which each factor influences the decision process. It is this question that the discrete choice experiments were designed to answer.

Within this component of the study we designed a survey to be undertaken with physicians involved in the decisions around the treatment of HCV. We acknowledge that at present many tertiary care centres will already have treatment protocols in place, but the interest here lies in teasing out the details of some of these protocols, gaining insight into the unwritten judgements that are made in the application of the protocols, and exploring how protocols may change if the treatment regimens on offer were to differ significantly in the future. We therefore interviewed both the key opinion leaders in treatment centres (who are likely to be influential in setting the protocols) and the physicians and specialist nurses who are involved in the day-to-day delivery of treatment (and are interpreting how to apply treatment protocols).

2.5.1 Design of the choice experiments

Discrete choice experiments provide a method for gaining quantitative insights into the influence of different factors on decisionmaking. This method is grounded in economic theory, and there is a growing literature around the use of discrete choice experiments and

[6] See for instance Aitsi-Selmi and Williams (2010) and NHS Education for Scotland (2010).

their application within healthcare research (Lancsar and Louviere, 2008; de Bekker-Grob, Ryan and Gerard, 2012). Within a discrete choice experiment respondents are asked, in a survey context, to consider a range of hypothetical choice scenarios, each described by specific attributes, and indicate the decisions that they would make in these scenarios. This provides an approach within which decisionmaking can be discussed in a structured manner with a large sample of individuals with a focus on the trade-offs made. One of the strengths of discrete choice experiments is the constrained closed nature of the task; respondents are given a scenario and then asked what they would do. As a result, respondents are forced to make trade-offs as they can't have the best of everything and have to make pragmatic judgements about how would respond in each situation. By asking a range of carefully chosen scenarios with an appropriate variation in each attribute within the scenario it is possible to collect data that allow the estimation of econometric models that give insight into the weight placed on each attribute when making the trade-offs. Such a model can then be used for forecasting, and in this study for forecasting physicians' treatment decisions.

Our survey included two discrete choice experiments to gain insight into the two key decision points made by physicians and those who treat HCV:

- the decision about when to start therapy
- the decision about when to make changes to the treatment regime of patients already on a therapy regime.

In each case we described a patient profile to the physician using a range of attributes that briefly characterised the patients' clinical history, demographic characteristics and social characteristics.

In the first experiment we asked the physician to consider a new patient and provided them with information about that patient, their background and current condition. They were then asked whether they would decide to commence HCV treatment. Each physician was asked to consider a range of different patient profiles.

Having completed this task the physician was then asked to consider the situation where they have patients already undergoing therapy with pegylated interferon alfa and ribavirin, who may be responding at different levels to that therapy with varying side-effects and adherence levels. Again, in this experiment they were given the profiles of the patients and informed of the time period for which they had been receiving treatment. They were asked whether they would: continue with the current treatment, change the dosage prescribed, or decide to stop therapy. As with the first experiment, each physician was asked to consider a range of different patient profiles.

The choice experiments were embedded within a wider physician survey, which also collected information on the physician's background and level of experience, the setting within which they were working, and their views on the ways that practice may change over coming years. This survey was conducted as either a telephone interview or web-based survey, depending on the physician's seniority and preferences, and took approximately 45 minutes to complete. Physicians were reimbursed for their time according to fair market value. We aimed to recruit 50 respondents in each of the four countries within the study.

The two choice experiments at the core of the survey were based on a statistical experimental design, which allowed the isolation of the influence of each of the patient characteristics on the treatment decisions made. Each experiment covered 81 different choice scenarios, which were determined using an orthogonal main effects fractional factorial design. These designs were divided into nine blocks of nine scenarios, and each respondent evaluated one block (nine scenarios). A blocking approach was used which minimised the correlation between each individual attribute and the block selected; this ensured that each respondent was presented a range of scenarios with differences across the various patient characteristics. Further details of the patient characteristics and their levels are provided in Chapter 6.

From the data collected we set up a series of econometric models, within the discrete choice modelling framework, to explain the importance placed on each of the characteristics when making each of the treatment choices. By collecting data across different treatment centres, different clinician types and different country settings it was possible to explore the extent to which each of these factors impacted on the decisions made.

2.5.2 Discrete choice models of decisionmaking

The discrete choice models that have been developed are based on random utility theory and aim to replicate the stated choices made by physicians during the survey. The models are based on the principle that each respondent acts to maximise their utility – chooses the treatment alternative which they believe is the best of those on offer given the circumstances within the scenario under consideration. Each choice alternative, *i*, in a discrete choice model is specified with a utility function for respondent, *n*, such that:

$$U_{ni} = V_{ni} + \varepsilon_{ni}$$

V_{ni} is the systematic or measurable utility that the individual *n* receives from adopting choice *i*. In addition to these observed components, the utility functions contain error terms ε_{ni} that account for the unobserved components of utility.

McFadden (1974) showed that working from the assumption that the individual is a utility maximiser when considering the alternatives, *j*, available to them, i.e.

$$P_{ni} = \text{Prob}(V_{ni} + \varepsilon_{ni} > V_{nj} + \varepsilon_{nj} \ \forall \ j \neq i)$$

and that the error terms ε_{ni} are assumed to be independent and identically distributed with a Gumbel distribution, that it is possible to derive a succinct closed form expression for the logit choice probability:

$$P_{ni} = \frac{e^{Vni}}{\sum_j e^{Vnj}}$$

As there is an assumption of independence between observations,[7] the likelihood function is given by the product of the model probabilities that each individual chooses the option

[7] An ex-post correction for the violation of this assumption was made through bootstrapping the models to correct for any specification error introduced through the consideration of multiple responses from each respondent.

that they are actually observed to select; and the best fit of the model to the data can be established through the maximisation of the likelihood function.

The models have been developed by exploring a range of different specifications of the utility equations used to represent the factors influencing physician treatment decisions. First, the extent to which interval attributes (e.g. patient age, platelet count) were valued linearly was tested.[8] Second, we systematically compared model forecasts with observed choices to test whether physician or health system characteristics affected whether physicians were more or less likely to treatment, independent of the patients presented. Finally, we systematically compared model forecasts with observed choices to test whether physician or health system characteristics affected whether physicians were more or less influenced by particular patient characteristics when deciding whether to treat.

The output from each model is a set of coefficients that quantify the influence that each factor has on the likelihood of treating a patient and continuing treatment. However, the magnitude of the influence of these, and how they work in combination in influencing treatment decisions, is not immediately obvious from examination of the coefficients alone. A spread sheet was therefore produced that uses the utility functions and coefficients from the estimated models to calculate the probabilities of each possible outcome, and presents these separately for each of the four countries within the scope of the study. This interface can then be used to examine how the nexus of patient attributes combine to influence the probability that specific profiles of patients will, or will not, be treated.

2.5.3 Caveats

In interpreting the findings from the discrete choice experiments it is important to recognise that these are based on a framework which assumes rational decisionmaking and consistency in treatment decisions. For the purpose of estimating the models of the choices made within these hypothetical choice scenarios the assumption has a good foundation; we controlled the information which physicians were asked to consider and have estimated models that are consistent with the choice-making behaviour observed. However, as in all such studies, there remains a risk that attributes that play an important role for some physicians may not have been included within the experiment developed within this study. We believe that the process we have adopted in reviewing the literature and consulting experts in the field will have minimised the possibility that important attributes have been omitted. There remains the possibility, however, that in real patient treatment environments there are other inter-personal factors that may influence the decisions of physicians. We have tried to capture these as best as possible through the incorporation of "patient motivation" and "patient adherence", but we recognise that in real treatment environments physicians may exercise discretion for some specific patients and make choices that on the face of it run counter to the rational decision rules that they may otherwise be applying.

It is also important to recognise that the preferences and decision behaviour that are captured within the model are those that relate to the sample of physicians we have interviewed. In any empirical data collection process it is necessary to bear in mind that there may be some groups that have declined to participate in the process and are therefore

[8] Details of the full range of attributes included in the experiments are provided in Section 6.1

not covered within the analysis. In this respect it is worth noting that a significant investment was made in recruiting physicians to the study, with direct bespoke telephone contacts made to lists of physicians working within this area. The actual universe of physicians within each country is relatively small, so in collecting a sample of this size the probability of omitting a large segment of people with differing views is somewhat smaller than for many studies. However, the reader should be aware that the findings relate to the sample (whose characteristics are reported in Section 6.2) and may require care in their interpretation if it is believed that some key groups of physicians have been omitted.

2.6 Workshop and scenario development

A one-day workshop was held at RAND Europe (see Appendix D for the agenda). Participants included the RAND Europe and Baird's CMC project team, the GSK project team and experts from the different European countries considered in the study. The first half of the day was focused around presentation of the emerging findings of the study and the discussion of those findings. The second part of the workshop was dedicated to the preparation of the scenario development. A scenario can be described as a *coherent* picture of a *plausible* future. Scenarios are used to deal with the uncertainty about what the future could bring. A scenario in the policy analysis world can be a preferred future, an unpreferred future, or just a possible future – as long as it is plausible. In this sense, it can serve as an innovative platform for continuing validation of the findings of the discrete choice experiment, and development of shaping actions which could improve treatment prospects and patient outcomes. Prior to the workshop, a list of key factors influencing physicians' decision to commence and continue treatment of patients was determined using the outcomes from the discrete choice experiment. These factors were then systematically categorised with the experts at the workshop, based on the perceived level of impact and the level of uncertainty of the factor. The scenarios then focused on those factors that had a high impact and high level of certainty, and these were used to develop key shaping actions which could be adopted to support the development of each situation described. By retaining factors that have a high impact, and a high level of certainty, and varying the combination of these, a set of scenarios was composed and shaping actions suggested.

2.6.1 Caveats

It is important to note that the scenario exercise requires differentiation between different futures which have been deliberately created to present polarised future worlds. The actual future will probably be a mix of the different scenarios, e.g. including features and elements from across the scenarios. Thus, the point of the scenarios is to promote thinking and cross-cutting insights about future possibilities and how our actions today might shape the future. In addition, uncertainties and the unknowns are used in the scenario as a means to build variations. They may not be realised and therefore potentially hinder the relevance of the work presented.

CHAPTER 3 Literature review identifying the diversity of factors influencing treatment decisions

3.1 Summary

Our analysis of the literature suggests two broad categories of factors that influence treatment decisions (initiation, dosage adjustments and termination): the *profile of the user* (patient) and the *features of the health system*. Within each of these categories, there are various sub-groups of influencing factors. For the user profile they include clinical characteristics; side-effects experienced as a result of the treatment, response to treatment, related conditions and comorbidities; and user-behaviour-related factors and demographic characteristics. Those related to health system factors include issues related to health financing; regulation; health system organisation, access to care and care quality; and service provider characteristics. These are expanded below.

It is important to note that to the best of our knowledge we did not find any literature comparing the relative influence of different factors driving the decisions physicians make. Multiple and diverse user profile factors are considered in national and European level clinical practice guidelines (e.g. clinical, behavioural), but guidelines do not equate to the ultimate decisions physicians make in practice and do not illuminate how and why they reach them. Moreover, evidence on adherence to guidelines is scarce, piecemeal and fragmented. In general, the focus on the *process* of decisionmaking by service providers (rather than the decision itself) is very scarce in the literature. Hence, there is a need for further primary research with the service providers.

Table 3.1 summarises the key factors which can influence decisionmaking in HCV, as discussed in the literature reviewed. In the sections below we discuss each of these in further detail.

Table 3.1 Summary of key factors influencing decisionmaking on HCV treatment

Feature influencing treatment decisions	Sub-categories and examples
Clinical factors	Viral genotype Haematological abnormalities (e.g. TCP, anaemia, neutropenia, drugs to increase platelet counts such as eltrombopag)
Other comorbidities and related conditions	HIV, obesity, diabetes, hepatitis B, coronary heart disease, rheumatoid arthritis, depression, renal disorders, HCV-related cirrhosis
Side-effects	Less severe: fatigue, depression, irritability, sleeping disorders, skin reactions and dyspnea; haematological side-effects discussed above Unusual or severe; examples include seizures, bacterial infections, autoimmune reactions, interstitial lung disease, bone marrow aplasia or idiopathic TCP
Special population groups, demographic factors and user behaviour	Injecting drug users, alcohol-dependents, prison inmates, and migrants Age-related groups (e.g. children, older people)
Socio-demographic factors	Income levels, deprivation, social inclusion, geographical and administrative regions
Patient-behaviour-related factors	Refusal of liver biopsies; issues related to adherence to antiviral therapy; and wider behaviour related to substance misuse, information and awareness about effective treatment strategies
Health financing and cost-effectiveness	Contextual factors influencing cost-effectiveness: health system resources; burden of disease; specific patient subgroups (genotype, comorbidities, age); drug price Ability to predict response rates (tools and resources available)
Regulation and guidelines	Awareness of guidelines Adherence to guidelines by health care professionals
Access to care and care quality	Eligibility criteria Physician education levels Access to educational interventions to improve HCV practice and alleviate fears and/or discriminatory practices Preconceptions and fears Collaboration between health care professionals and wider health system stakeholders Patient information and awareness about care pathways and options State of medical data recording and information systems to improve referral pathway performance and care management network Clinical and behavioural profiles of users (e.g. special population groups, side-effects, non-responsiveness and comorbidities)

3.2 User profile-related factors influencing HCV treatment

High level summary

- **Clinical factors, comorbidities and side-effects**: The literature on the relationship between clinical factors and treatment of HCV is vast. The key clinical factors addressed include the influence of viral genotypes, haematological abnormalities (e.g. TCP), related conditions and comorbidity. The literature we reviewed focused on conditions including TCP, anaemia, neutropenia, HCV-related cirrhosis, obesity, diabetes and insulin resistance, and HIV. Agents such as eltrombopag, which increase platelet counts in patients with HCV, can enable the initiation of antiviral therapy but it is important to address adherence challenges, potential side-effects and to consider cost-effectiveness in a particular health system context. Side-effects of treatment are also reported in numerous guidelines and in the wider literature, and most side-effects of PEG IFN/RBV can be managed, although careful monitoring is needed.
- **Special patient groups, socio-demographic factors and user behaviour**: The literature examines the influence of numerous factors related to special patient groups, user behaviour and demography on antiviral HCV treatment decisions and outcomes from therapy. Special population groups examined include injecting drug users, alcohol-dependents, prison inmates and migrants. Examples of socio-demographic factors addressed include income levels, deprivation and social inclusion. Behaviour-related factors include refusal of liver biopsies, issues related to adherence to antiviral therapy, and wider behaviour related to substance misuse. Collaboration between disciplines and professions, education and peer support are seen as important determinants of successful HCV treatment outcomes in special population groups.

3.2.1 Clinical factors, comorbidities and side-effects

Haematological abnormalities

***Core messages**: Haematological abnormalities (e.g. anaemia, neutropaenia and TCP) are complicating factors in the management of disease in patients with HCV and chronic liver disease (Afdhal and McHutchinson, 2007). A number of studies focus on agents which can increase platelet counts in patients in order to allow antiviral therapy. In general, these studies identify eltrombopag as a promising agent, but the evidence on cost-effectiveness and adherence issues associated with eltrombopag is fragmented. Side-effects associated with eltrombopag are also discussed, though these are generally seen to be of a nature which does not warrant discontinuation of treatment, in a majority of patients.*

In a recent study, Giannini et al. (2012) found that haematological abnormalities (e.g. anaemia, neutropenia and TCP) hinder the initiation of antiviral therapy in one in every seven patients who would otherwise be eligible for treatment. In a review of evidence from clinical trials (predominantly), Afdhal and McHutchison (2007) analysed the limitation of traditional therapies for addressing TCP (e.g. safety and economic factors associated with

platelet transfusion) and effects of novel orally available therapies such as eltrombopag.[9] A later paper by Afdhal et al. (2011) evaluated the ability of eltrombopag to increase platelet counts and allow initiation and maintenance of antiviral therapy in patients with TCP and chronic HCV. Discussing the final results of Enable 1, a phase 3, multicentre study, the authors concluded that eltrombopag increases platelet counts in these patients to levels which could enable 95% of them to initiate antiviral HCV therapy, and subsequently to maintain antiviral dosage and achieve a SVR. Similar findings are reported by McHutchison et al. (2007) for patients with TCP due to HCV-related cirrhosis, and by Stasi et al. (2009) and Mac Nicholas and Norris (2010).[10]

However, Bussel and Pinheiro (2011) reported challenges with adherence to eltrombopag treatment due to administration-related issues (it must be taken every day apart from specific meals containing high levels of calcium). Corman and Mohammad (2010) warned against side-effects (hepatotoxicity), and identified higher costs associated with eltrombopag than corticosteroid-based treatments for low platelet counts as important factors to consider in decisions on treatment. However, Danish et al. (2010) emphasised that the commonly reported side-effects are generally of insufficient severity to warrant discontinuation of the drug. Schelfhout and Kauf, (2011) adopted a modelling approach and concluded that eltrombopag is a cost-effective option for treating patients with TCP and chronic HCV. No evidence was found on the impact of TCP on quality of life.

Other related conditions and comorbidity

Core messages: *The literature emphasises the importance of weight-loss on HCV antiviral treatment outcomes. HIV co-infection is also studied, with evidence of considerable under-treatment of this patient sub-group (e.g. in Germany, Austria) and/or substantial delays in treatment initiation (e.g. in France), as well as reports of a need to address inequities in access to care for this patient group through improved collaboration between hospitals and general practitioners (GPs) (e.g. in France). A number of Spanish studies advocate treatment of HIV co-infected patients and show reductions in mortality in this group. Another commonly addressed comorbidity is depression (and psychological disorders more widely), with evidence suggesting the need for close collaboration between specialties (e.g. hepatology, psychology, psychiatry) to improve HCV treatment outcomes in this patient group. Renal disorders are also discussed, as antiviral HCV therapy can be poorly tolerated in patients with kidney disorders and HCV. Other reported comorbidities include coronary heart disease, rheumatoid arthritis, diabetes and hepatitis B (HBV) as some examples. Cirrhosis and liver disease are frequent co-conditions as well, but often there is a causal relationship between HCV and the development of more severe cirrhosis and liver disease.*

Adinolfi et al. (2011) examined treatment strategies for individualising HCV therapy and the influence of factors such as *diabetes and weight*-related comorbidities. They found that weight loss is a critical factor influencing treatment outcomes and the achievement of SVR, and that statins seem to improve response rates to treatment with PEG IFN/RBV. Evidence on insulin sensitisers is inconclusive. The adverse impacts of being overweight on

[9] As well as AKR-501, peptidic agonists AMG-531 and Peg-TPOmp, and small engineered antibodies.

[10] Mac Nicholas and Norris (2010) found that treatment of haemophilic patients more widely with novel agents (e.g. eltrombopag) can be effective and allows antiviral therapy initiation.

antiviral treatment outcomes are also confirmed by other studies (e.g. Delgado-Borrego et al., 2010).

Angeli et al. (2011) focused specifically on patients with chronic HCV and *HIV co-infection*, to examine the eligibility and feasibility of maintaining antiviral HCV therapy in this group through retrospective analysis. They identified common barriers related to contraindications (e.g. substance abuse, concomitant conditions) and low adherence. They suggested that many of the barriers to eligibility and feasibility of treatment are modifiable. Baumgarten et al. (2009) found evidence of considerable under-treatment; they focused on the initiation and deferral of therapy in patients with HIV and assessed the gap between guidelines and actual practice drawing on data from a multicentre study of 12 treatment centres in Germany. Considerable under-treatment was also reported by Reiberger et al. (2011), drawing on a large cohort study in Germany and Austria. Rockstroh et al. (2008) advocated for more bespoke approaches to the duration of HCV therapy in patients with HIV. In a recent French study, Salmon-Ceron et al. (2012) examined delays in treatment of this patient group, and aimed to identify the correlates of access to HCV treatment in patients with HIV. They used three-year follow-up data from the HEPAVIH ANRS-CO13 nationwide French cohort, which enrolled patients living with HIV and HCV, and found that networks between hospitals and GPs can play a key role in reducing existing inequities in access to HCV care in this population group. In a Spanish study, Sanmartin et al. (2012) evaluated the factors associated with overall mortality and liver decompensation in HIV and HCV-co-infected patients with liver fibrosis stage. They found HIV/HCV-co-infected patients with poor predictors of survival are candidates for intensive clinical management and strongly recommended treatment of this group because it significantly decreases mortality. In an earlier Spanish study Arizcorreta et al. (2004) showed that haematological abnormalities such as low platelet count in this patient group did not influence decisions to start or stop treatment. Berenguer et al. (2012) conducted a cohort study of 19 Spanish centres (from 2000 to 2008) and found that the elimination of HCV following treatment with INF-RBV in HIV-co-infected patients is associated with a reduction of liver-related problems and a reduction in HIV progression and mortality that is not related to liver disease. The authors advocated for treatment to start as early as possible.

The literature also contains studies examining HCV patients with symptoms of *depression* (e.g. Golden et al., 2005; Lang et al., 2009). For example, Lang et al. (2009) studied the management of psychiatric disorders and addictive behaviours of patients with HCV in France, and through retrospective interviews with 101 clinicians as well as by examining patient files, identified the lack of collaboration between hepato-gastroenterologists and psychiatrists as a problem for treatment outcomes. Lang et al. (2010) highlighted the importance of close monitoring of patients with associated *psychiatric disease* to ensure antiviral treatment adherence.

Renal conditions are also a comorbidity discussed in the literature that we assessed. For example, in a Romanian study, Covic et al. (2006) identified that PEG INF alpha treatment is poorly tolerated in *dialysis patients* causing low adherence and discontinuation of therapy. Tang et al. (2003) suggested that PEG INF/RBV can be considered in patients with acute HCV infection following *renal transplantation.*

Treatment of patients with *rheumatoid arthritis* and chronic HCV was discussed by Giannitti et al. (2009) and tumour necrosis factor rheumatoid arthritis treatments were found to be safe for use in combination with Cyclosporine A for HCV. *Coronary heart disease and HBV* are also comorbidities addressed in EU guidelines (EASL, 2011).

Side-effects experienced as a result of the treatment

***Core messages**: Evidence from the literature reports on side-effects associated with PEG IFN/RBV and advocates careful monitoring. The majority of side-effects are considered manageable in most cases.*

Clinical factors weigh heavily in treatment recommendations on antiviral dosage and duration (e.g. Annicchiarico et al., 2012) and point to the need for careful monitoring of adverse events in patients with different clinical characteristics. Calvaruso et al. (2011) reviewed evidence on side-effects associated with antiviral therapy and their influence on the initiation, continuation and adaptation of treatment. They emphasised the importance of screening for adverse risk factors by physicians to decrease chances of treatment discontinuation and enable effective adaptation strategies. They advocated the creation of guidelines for treatment in the case of specific side-effects. Side-effects associated with the common standard of care are reported in various treatment guidelines, and include:

> fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnea. Hematological and biochemical side effects of pegylated IFN-a and ribavirin include neutropenia, anaemia, TCP, and ALT flares. Unusual or severe side effects include seizures, bacterial infections, autoimmune reactions, interstitial lung disease, a neuroretinitis, bone marrow aplasia or idiopathic TCP. Patients should be advised of the risk of foetal malformation with RBV and the need for contraception for 6 months beyond treatment. Patients treated with pegylated IFN-a and ribavirin should be seen at a minimum of weeks 4 and 12 after initiation of treatment then at a minimum of every 12 weeks until the end of treatment for both efficacy and side effects, and 24 weeks after the end of therapy to assess the SVR (EASL, 2011).

Da Silva et al. (2009) examined acute pancreatitis as a complication of PEG IFN/RBV treatment but emphasised that it is rare, and that clinical signs should be monitored and identified early.

3.2.2 Special patient groups, socio-demographic factors and user behaviour

Special population groups

***Core messages**: A vast body of literature focuses on special population groups, and in particular on substance misuse (e.g. injection drug use, alcohol-dependence). The key message from this literature is a need for integrated approaches and collaboration between specialists from different disciplines and sectors (e.g. hepatology, psychiatry, psychology and social care). Some studies also address issues related to access to care by prison inmates and migrants, highlighting that many of the barriers to effective treatment and care are modifiable. There appears to be comparatively less focus on children and HCV treatment, although this may be an artefact of our literature identification procedure and the need to prioritise and balance across multiple criteria in selecting literature and abstracts to review.*

For example, Almasio et al. (2011) provided information on HBV and HCV infections among *drug users, prison inmates and migrants* in Italy, and emphasised the importance of considering social, environmental and clinical factors, as well as adherence to national and

international guidelines, when making treatment decisions and selecting candidates for therapy in special population groups. The authors found short treatment durations to be enablers of adherence and a vehicle for limiting adverse events. They reviewed previous studies and guidelines, and created new recommendations. Among other factors these emphasised the importance of understanding the level of a patient's social integration, given the importance of wider social support structures for treatment outcomes, and also the importance of considering cost-efficacy and cost–benefit analysis in decisions on treatment. Almasio et al. (2011) argued for the importance of identifying predictors of adherence such as income levels; lack of access to care; linguistic, cultural and education issues; and social support structures. Multidisciplinary and transcultural counselling, peer education activities and specific training for healthcare workers were also recommended by the authors, so as to improve adherence. Challenges in access to medical care for immigrant groups are well known across therapeutic fields and disease areas. Perhaps somewhat surprisingly, Niederau et al. (2012) found migrants have a better treatment uptake than natives (and acknowledged they are not able to explain this particular finding). Lisker-Melman (2011) identified that lower efficacy rates in some categories of difficult to treat patients, including genotype 1 black individuals, can be improved with triple therapy (with add-on direct acting antiviral agents), but that there can be problems with adverse events.

Reimer et al. (2005) reviewed and rated national and European guidelines for HCV treatment in injecting drug users, and identified the need for qualified guideline processes at the national level, and renewal of guidelines at the EU level – highlighting that only France and the EU provided high quality guidelines at the time for *drug users and prison inmates*. A year later, Saiz de la Hoya-Zamacola et al. (2006) presented expert recommendations for the diagnosis and treatment of prison inmates in Spain. Almasio et al. (2011) advised that inmates' alcohol consumption should be monitored in order to prevent, diagnose and treat HCV. Remy et al. (2006) focused specifically on *prison inmates*, and through a prospective study involving 37 medical units in French jailhouses concluded that treatment for HCV in French jailhouses is doable and successful. In a Spanish study, de Juan et al. (2011) examined practices at 26 prison centres and identified a lack of motivation and awareness in patients, as well as adverse events, to be the main reasons for not initiating therapy by inmates. However, the authors argued that the barriers to treatment are modifiable factors that depend on patient education and adequate medical care.

Numerous studies across geographical contexts emphasise the *need for cooperation between professional bodies*, so that early treatment with HCV antivirals is complemented with treatment and monitoring of mental disorders and drug abuse (e.g. Backmund et al., 2005; Belfiori et al., 2009; Lang et al., 2009). One particular challenge is the lack of collaboration between specialists in HCV treatment and in the treatment of mental health issues (e.g. psychiatrists). Lang et al. (2009) identified a significant divergence between the clinical practices of physicians specialised in the treatment of viral hepatitis and guidelines of the time, which recommended a multidisciplinary approach to patient management. They reported that psychiatric disorders significantly influence the decision of whether or not to initiate antiviral treatment or to interrupt it. They found this to be partially related to the absence of a standard method for assessing a disorder and its impact on the tolerance

and efficacy of antiviral therapy. Robaeys (2009) emphasised the need for *integrated strategies combining education, case-management and peer support* to improve care and treatment of HCV-infected substance users, focusing in particular on injecting drug users. Le Lan et al. (2012) focused on *alcohol-dependent patients*, and challenged French guidelines, which recommend a six-month wait before treating this population group. They found that treatment is efficient despite ongoing alcohol consumption; that a multidisciplinary treatment approach enables SVR and has positive effects on addiction behaviours; and that treatment should be started early as the disease can evolve rapidly with alcohol abuse.

Insights on the efficacy, safety and cost–benefit of HCV treatment *in children* are inconclusive (El Sherbini, 2010). By contrast there is evidence of under-treatment of the elderly (e.g. Brant et al., 2005; Agostini et al, 2007).[11]

Other user behaviour and demography-related factors

***Core message**: Our literature review also identified studies focusing on patient-choice-related factors (e.g. adherence issues) and on relations between deprivation and access to HCV care.*

For example, in a study of patients in France, Bonny et al. (2003) surveyed 250 physicians and found that *patient refusal of a liver biopsy* restricts the management and therapy of HCV infection.[12] Giannini et al. (2006) proposed the use of inexpensive parameters such as the aminotransferase/alanine aminotransferase (AST/ALT) ratio and platelet count to reduce the need for liver biopsies. *Adherence* to antiviral therapy and associated therapies is also raised in the literature. For example, administration-related issues associated with eltrombopag can hinder adherence (Bussel and Pinheiro, 2011).

Astell-Burt et al. (2012), building on data from 1991 to 2006, used quantitative geographic information system and logit regression analysis to examine *whether length of time spent travelling to the treatment centre* influences patients' decisions on antiviral treatment and follow-up, but did not find supportive evidence for this. However, they do find that in a UK context, a history of *injecting drug use* is a strong predictor of non-attendance of appointments at specialist centres and of loss of follow-up. Follow-up was also found to be less likely with patients living in *deprived areas*.

[11] A US consultation recommending HCV screening in older individuals in the absence of predisposing causes or risk factors has just been launched. See http://www.regulations.gov/#!documentDetail;D=CDC-2012-0005-0002.

[12] This is no longer an issue as in 2003 a liver biopsy was regarded as essential in planning therapy, whereas now it is more rarely conducted in favour of non-invasive processes.

3.2.3 Health system factors influencing HCV treatment

High-level summary:

- *Finance related*: Cost-effectiveness is an important consideration in treatment decisions and the evidence base of cost-effectiveness of HCV therapy regarding decisionmaking is fragmented and inconclusive. Cost-effectiveness is context dependent, varying by disease burden, user and health system features. There is also a scarcity of evidence on the cost-effectiveness of eltrombopag. Better predictors of treatment responses could inform cost-effectiveness.
- *Guidelines and regulation*: Evidence on adherence to national and EU-level treatment guidelines is limited, and there is a gap in studies comparing differences between guidelines of different countries, and between countries and EU and international guidelines.
- *Access, care quality and treatment nature*: Addressing inequities in access to care and care quality requires collaboration between health care professionals and wider health system stakeholders, educational interventions geared towards physicians and patients, better information recording, and sharing within referral and care management pathways. GPs, specialists and nurses (as well as other health professionals in special population groups) are all involved in the treatment of patients with HCV, but their comparative role across different geographies is not clear from the literature. Decisions on treatment duration and whether to start, adjust and discontinue treatment are related to clinical and behavioural features of special population groups, side-effects, non-responsiveness and comorbidities, and physician's specialism.

3.2.4 Health financing and insights on cost-effectiveness

***Core messages**: Our review did not focus on analysing different health-finance models in Europe, as this was outside the scope of the study. However, we did examine general cost-effectiveness insights from the literature. Evidence on the cost-effectiveness of HCV anti-viral therapy is inconclusive, and appears to be context dependent on factors such as the burden of disease, health system resources, and specific subgroups of patients (e.g. genotype related, cirrhosis related, age related, weight related). Evidence on the cost-effectiveness of treating TCP in patients with chronic HCV is also inconclusive and there is a scarcity of economic evaluations at European level. There is an evolving body of literature on predicting response rates to treatment and this is related to efforts for cost-effectiveness and improved patient outcomes.*

For example, Davis et al. (2010) in a rare pan-European study (covering France, Germany, Italy, Spain and the UK) documented "real-world" utilisation and costs of PEG IFN/RBV therapy emphasising that they are costly, and that where the burden of HCV is high, public health systems should consider these costs when considering alternative treatments. However, Grishchenko et al. (2009) performed a cost-effectiveness analysis in the UK (using information from the Trent HCV database), and concluded that treatment is generally cost-effective, but that there are variations according to sub-group, with lower

cost-effectiveness in older patients and in genotype 1 patients with cirrhosis.[13] They used a Markov decision model to estimate the lifetime cost per quality-adjusted life year (QALY) of antiviral treatment compared with no treatment. Siebert et al. (2009) analysed German guidelines and perform a cost-effectiveness evaluation on different treatment strategies for chronic HCV. They discussed the importance of tailoring treatment efficiently to genotype, bodyweight and early viral response profiles of patients, and the challenges of trying to generalise cost-effectiveness results across geographical contexts, given differences in socio-demographic profiles, distribution of patients' clinical characteristics, utility profiles, resource use and pricing. Martin et al. (2011) modelled cost-effectiveness of different HCV treatment strategies for injecting drug users and concluded that the optimal strategy depends on the priority goals (e.g. relative weight of cost-effectiveness, prevalence reduction, health utility and coverage).

The evidence of cost-effectiveness of treatments for TCP specifically (as a commonly related condition in patients with HCV) is inconclusive. For example, Afdhal and McHutchison (2007) emphasised that strategies to address TCP in patients with HCV, through platelet transfusions (and increase platelet counts to enable antiviral therapy), have not only safety but economic-related limitations when compared with treatments like eltrombopag. However, Corman and Mohammad (2010) identified higher costs associated with eltrombopag than corticosteroid-based treatments for low platelet counts as important factors to consider in decisions on treatment of conditions like idiopathic thrombocytopenic purpura. Schelfhout and Kauf (2011) adopted a modelling approach and conclude that eltrombopag is a cost-effective option for treating patients with TCP and chronic HCV. They stated that patients treated with eltrombopag are more likely to complete antiviral therapy and that this in turn leads to increased quality of life and decreased future costs over a lifetime. Brown (2007) identified blood monitoring, hospital stay peri-procedures, therapy needed to increase platelet count, complications of therapy (e.g. bleeding, transfusion reactions) and inadequate therapy for low platelets as cost drivers. Poordad et al. (2011) also identified that HCV patients with TCP have significantly higher costs of healthcare than patients without TCP, due to greater hospitalisation numbers, emergency room, ambulatory care or outpatient visits. However, the study acknowledged difficulties in separating HCV specific and chronic liver-disease-related costs, and limited EU data (evidence comes from US studies[14]). There are, however, limited economic evaluation data for Europe (US evidence prevails), and it is also difficult to dissociate costs related specifically to HCV as opposed to chronic liver disease.

Predicting response and non-response to antiviral therapy in specific patient populations is also investigated, and is related to cost-effectiveness and quality improvement. A number of studies focused on gene expression and prediction (e.g. Selzner and al., 2008). Chevaliez and Assellah (2011) identified that up-regulation of interferon stimulated genes is common in genotype 1 non-responders, and suggested a need for service providers to *focus on identifying non-responders in advance of therapy* using combinations of genetic, clinical,

[13] "For genotype 1 cases with mild or moderate disease, and younger cirrhotic patients (aged 40 or less), costs per QALY remained below £20,000 ($40,000 or €29,000). For genotype 1 cases with cirrhosis aged 50, the mean cost per QALY rose to over £60,000 ($120,000 or €87,000)" (Grishchenko et al., 2009).

[14] Communications with GSK.

biochemical and histological data. Glisic et al. (2011) identified a simple bioinformatics criterion which they suggested could be used to predict response rates to antiviral therapy with PEG IFN/RBV. Barreiro et al. (2010) drew on findings from a Spanish cohort study in two referral clinics and found that IL-28B *single nucleotide polymorphisms* predict sustained virological response to re-treatment with PEG IFN/RBV therapy in more difficult to treat patients with HCV 1–4 genotypes. Herber and Berg (2011) identified *advanced fibrosis or cirrhosis as negative predictors* of treatment response to new protease-inhibitor base re-treatment of patients. Thomson et al. (2008) identified differences in response rates between different subgroups (especially related to genotype, age and disease stage) and argued that *probability modelling* can be a useful tool in predicting response rates and individualising patient management. They argued that much of the evidence informing clinical and patient decisions is only available in an aggregated format, using summary statistics (e.g. odds ratios), and tends to address this limitation by identifying key prognostic factors associated with achieving an SVR, and presenting the results as predicted probability of response for the key patient groups. In particular their predicted probabilities suggest early treatment of patients with HCV disease, particularly those with genotype 1. In a Spanish study, Buti and Casado et al. (2006) examined the financial *impact of two different ways of evaluating early virological response and predicting likelihood of attaining sustained virological response* in HCV genotype 1 patients being treated with PEG IFN/RBV. They found that HCV core antigen-based testing is more cost-effective than HCV RNA testing or no testing at all.

Vezali et al. (2010) reviewed published evidence and also found that antiviral treatment in cirrhotic patients was less effective than in non-cirrhotic patients, but that eradication of the virus reduced liver complications and improved survival prospects of cirrhotic patients (particularly those with compensated cirrhosis).

3.2.5 Regulation and guidelines on treatment

***Core message**: Various national and EU level guidelines exist for treatment of HCV, but evidence on adherence to guidelines is limited. There is a scarcity of studies comparing differences between guidelines of different countries and between member states and EU level guidelines. Guidelines generally cover different stages of decisionmaking and types of disease (including diagnosis and pre-therapeutic assessment; and decisions to start, adapt or terminate treatment), as well as special population groups.*

Guidelines exist for our countries of focus – France, Germany, Italy, Spain and the UK – and at EU level.[15] The guidelines are comprehensive in covering who should be treated, how, for what duration, what factors drive termination (e.g. non-response in treatment naive patients, and side-effects and contraindications), and provide information on treatment for specific special population groups (e.g. with comorbidities). Frequent areas of focus for special population groups include renal failure and dialysis, extra-hepatic manifestations, pregnancy and lactations, substance abuse, autoimmune diseases, thyroid dysfunction, diabetes, coronary heart disease, hypertension, hemoglobinopathies, depression, psychosis, epilepsy and co-infections such as HIV and HBV. Other areas

[15] These are reported in Sarrazin et al. (2010), for Austria, Germany and Switzerland; EASL (2011) and Reimer et al., (2005) for the EU; NICE (2010) and HPA (2011) for the UK; Conférence de Consensus (2002) for France; Almasio et al. (2011), for Italy; Borbolla Garcia et al. (2012) and Ministry of Health, Social Services and Equality (2012), for Spain.

addressed by the guidelines include pre-therapeutic assessment of liver disease severity, treatment monitoring, dosage adjustment and stopping, and measures to improve treatment success rates. These include treatment adherence, supportive care and correction of cofactors, such as body weight, alcohol consumption, insulin resistance, growth factors and antidepressants (EASL, 2011). There is a scarcity of studies comparing differences between guidelines of different countries, and between member states and EU level guidelines (and adherence to those guidelines).

3.2.6 Access to care, care quality and system organisation

Core message: *The literature reviewed addressed issues of equity in access to care in health systems, service provider characteristics and their influences on treatment decisions, and factors influencing treatment durations in healthcare systems. The literature highlights inequities in access (e.g. in France, the UK) but some of the evidence is dated. However, more recent studies do emphasise the importance of greater collaboration between healthcare professionals to improve equity in access, uptake of services and patient outcomes. Related to this is a need for physician education to alleviate fears and reduce discriminatory practices, and to provide better medical data recording and information systems to improve referral pathway performance and care management networks, as well as patient education and support, in order to build shared understandings. It is evident that GPs, specialists and nurses are all involved in the treatment of patients with HCV, but their comparative role across different geographies is not clear from the literature reviewed.*

Agostini et al. (2007) examined management practices in the French health care system for antiviral-naive patients and found that only one-third of patients initiated antiviral treatment through GPs. They also found that women, older patients, patients with comorbidities (such as HIV) and patients on drug replacement therapy are less likely to be treated. In the UK, Parkes et al. (2006) compared treatment pathways for HCV patients, highlighting inequities in service provision and substantial variation in all aspects of the patient pathway. The authors examined workload, configuration and care processes of UK services at the time through a survey approach with consultant members of the British Association for the Study of the Liver, infectious disease consultants, and urologists and gastroenterologists. The key criteria considered by clinical service providers when determining eligibility for treatment were severity of the disease, comorbidities, age, genotype and gender. Reasons for patients' ineligibility were mainly ongoing drug or alcohol use, and reasons for patient refusal were mainly concerns over side-effects, and inconvenience of starting treatment. Funding for treatment was also cited as a barrier to care. The authors argued that there is a need for an expansion of clinical networks geographically and more resources to enable better uptake of services and more equitable delivery across the country, and highlighted challenges related to "postcode prescribing". Similarly and more recently, Tait et al. (2010) evaluated referral pathways and managed care networks (established to address barriers to treatment such as patients' refusal and perceptions, delay in obtaining specialist input, inadequate follow-up with primary care and a tendency not to treat past drug users) in the UK through a retrospective cohort study. They found that collaboration between health care professionals has a high impact on improving access to care in traditionally hard to reach populations, and that it does not require very high additional resources, but rather "working smarter". The importance of collaboration is also emphasised by others (e.g. Teoh et al., 2010). In a study on a special

patient group, Tompkins et al. (2005) conducted in-depth interviews with homeless injecting drug users with HCV and concluded that patient choice; confidentiality; pre- and post-testing discussion; and social, psychological and medical support and counselling are crucial in treating this patient subgroup.

Patients also need to be adequately informed in order to contribute to the decisionmaking process about their treatment. For example, D'Souza et al. (2005) found that patient education regarding cost-effectiveness of therapy is important for early cessation in non-responsive patients to be perceived as publicly acceptable. The authors examined patient preferences about cessation of therapy (asking patients if they wanted to withdraw from treatment after a 12-week failure of the treatment, having been told there was only a 3% chance of the treatment working after this time), and found that the assumptions of health care professionals about patient preferences were not always correct.

In a survey of primary care physicians in Italy, Cozzolongo et al. (2005) identified the need for *educational interventions geared at physicians* to improve general practice management of HCV infection. In a rare study focusing on nurses' attitudes (in Ireland) to the treatment of HCV patients, Frazer et al. (2011) reported that negative attitudes (e.g. fear of acquiring HCV and differing infection control practices) can lead to discriminatory practice and that education and training of nurses is needed to improve adherence to treatment guidelines. Univariate analysis of 981 nurse responses to a survey (in Ireland) had identified that younger nurses, those who had had contact with people with HCV, those who were educated to degree level and those who had experience working with addiction services had more positive attitudes to patients. In a UK context, Brant et al. (2005) focused on patients in the UK who had transfusion-acquired HCV and identified a risk of under-treatment at the time, and recommended the prompt initiation of treatment in this group and greater *awareness-raising activity* with GPs. *Poor data recording* by GPs can also be a challenge to optimal disease management. This was identified by Loguercio et al. (2011) in a study of chronic liver disease in Italy, although it did not directly focus on HCV. Sahajian et al. (2001) emphasised the importance of *medical follow-up* on clinical, biological, histological and virological data and the key role of the GP in the French context.

In a German study, Niederau et al. (2012) examined the nexus of reasons driving decisions against treatment of chronic HCV with antiviral therapy. The authors surveyed physicians and requested them to fill in a questionnaire prior to the treatment decision. This included questions on demographic data, the personal life situation of the patients, symptoms, virological data, laboratory data and data on co-infections. Physicians also provided information on reasons against treatment. The authors concluded that some reasons against treatment were related to *clinical factors (e.g. genotype, viral replication), but that others related to fears, socio-economic problems, age, comorbidity (e.g. HIV) and a lack of needed information* to make a decision by both physicians and patients. *Patient refusal was considered a significant barrier.* In an earlier French study, Bonny et al. (2003) also stressed the need for more training and support for decisionmaking about drug efficacy, and for more and better information to help manage physician or patient *fears about complications of treatment and other factors*. Wiegand et al. (2008) *argued for the need for specialist care* (internists with special experience in hepatology) in order to individualise treatment – given growing complexity of treatments.

3.2.7 Treatment duration and regime

***Core message**: Evidence from the scholarly literature on treatment duration focuses on early treatment, special population groups (e.g. co-infection) and different HCV genotypes. Insights focused on specific stages of treatment and decisions to start, adjust and discontinue treatment are related to clinical and behavioural features of special population groups, side-effects, non-responsiveness and comorbidities, and physician specialisms. There is some evidence that patient age and physician specialism influence adherence to treatment duration guidelines (there is a lower adherence by physicians who are infectious disease specialists and when dealing with older patient groups).*

Corey et al. (2010) drew on a meta-analysis and found that *early treatment* in *acute* HCV infection improves outcomes. They recommended a 12-week waiting period as optimal to assess whether spontaneous clearance has occurred. Hartwell et al. (2011) conducted a systematic review of clinical and cost-effectiveness of PEG IFN/RBV therapy and concluded that patients in three specific sub-groups (those co-infected with HIV, with low-viral load, and with rapid virological response) could be treated successfully with shorter durations, and that *shortened treatment* in these groups is likely to lead to QALY gains without prohibitive cost-increases. However, they emphasised the need for further randomised clinical trial evidence, in particular for people who have not responded to treatment or relapsed. By contrast, Lange et al. (2010) conducted a meta-analysis for another subgroup of patients, HCV genotype 1 slow responders, and identified that *extending the duration of treatment* to 48 weeks should be considered in difficult to treat patients. In a German study, Lehmann et al. (2004) found higher rates of spontaneous clearance for genotype 3 patients than in genotype 1 patients. Based on these findings they proposed that physicians should wait at least three months before initiating treatment, in particular for young, Caucasian men. Teoh et al. (2010) examined prospects of *individualisation of treatment durations*. For example, they provided evidence that dose-based treatment for 16 weeks is feasible in patients with genotype 2 and 3 infection, but that patients with cirrhosis, diabetes and older patients may need longer treatment (6–12 months). The authors also argued that preventing dose reductions and ensuring treatment completion requires monitoring and detection of disabling side-effects (clinical and psychological) and emphasised the importance of collaboration between specialist nurses, psychological therapists and other healthcare workers. Soriano et al. (2012) discussed decisions about treatment with new drugs, in the context of the dangers of the growth of resistance for non-responders, and the application of *early stopping rules*. They argued that there is a need for careful selection of candidates for therapy with protease inhibitors, close monitoring of drug adherence, proper management of side-effects and early application of stopping rules. Although insights focused on specific stages of treatment are not highly explicit in the literature, in general, decisions to initiate, adapt, discontinue treatment and/or adjust dosage are predominantly raised in the context of special population groups, side-effects, non-responsiveness and comorbidities.

Dalgard et al. (2011) examined physician adherence to guidelines for HCV (genotype 2 and 3) treatment in a study, including France, Germany, Italy, Spain and the UK, building on physician-reported data. They identified that adherence to duration guidelines is lower for older patients and when decisions were made by infectious disease specialists. Genotype, viral load and stage of disease did not predict treatment duration.

3.3 Conclusions

Overall the literature review provided a solid overview of the complexity of the treatment decision process, highlighting the relevance of a range of factors at the different stages of treatment decisionmaking. The evidence from the literature suggests that many user-related and health-system-related factors seem to have an influence on physicians' decisions. However, findings from the literature review remain limited as they do not provide information about the interplay of the different factors and the way they interact with each other. Evidence is also lacking on how physicians actually make decisions, and on the weight they attribute in practice to the various influencing factors. Those issues have been addressed in a qualitative and quantitative manner, through the subsequent key informant interviews and the discrete choice experiment tasks of the study respectively.

CHAPTER 4

Key Informant Interviews identifying and understanding the factors influencing treatment decisions

Key informant interviews provide a means to gain information and insight that is not easily accessible through information extracted from the published and/or grey literature. Expert judgement assessed through key informant interviews can be used to delineate what is known about the future of policy on a particular key health issue, and can help examine those issues and factors that may be difficult to measure or quantify.

The aims of the interviews were to enrich our understanding of factors influencing physicians about HCV treatment in the four countries of focus: France, Italy, Spain and the UK. The literature review, as reported in Chapter 3, highlighted a broad range of influences related to user and patient profiles and the health system. This was also confirmed by the interviews, which provided further contextual detail on how and why physicians make certain decisions about treatment initiation, adaptation and cessation. The literature on the topic is highly fragmented, and the interviews aimed to provide somewhat more integrated and comprehensive insights. The interview protocol therefore consolidated evidence on important factors from the literature, so that interviewees were asked about many diverse influences – ranging from clinical and behavioural aspects of the patient to broader health-system-related factors such as access and referral pathways, funding environments, access and quality of care.

Table 4.1 and 4.2 present a summary of the findings from the interviews which are supported by the detailed analysis of the interviews described in the rest of this chapter.

Table 4.1 Key insights from the key informant interviews about the user-profile factors influencing decisionmaking about HCV treatment

Factors influencing treatment decisions	Interview analysis[16]
Viral genotype	- Genotype was recognised as a factor influencing the nature of treatment. - No unambiguous evidence from interviews on how it influences treatment decision (to treat or not to treat a specific genotype).
Haematological abnormalities	- Haematological factors are important for treatment decisionmaking. - Careful monitoring of platelet counts is mandatory. - There is ambiguity between the countries about which haematological factors (anaemia, neutropaenia, TCP) are most frequent and important. - Evidence on adherence to guidelines about treatment decisions and platelet thresholds is ambiguous.
Comorbidities and related conditions	- Comorbidities are important influences on treatment decisions. - HIV, HBV, diabetes, renal disorders (patients on dialysis or with creatinine clearance <50 mL/min), depression, obesity, coronary disease, sarcoidosis, uncontrolled thyroid disease, epilepsy and pregnancy were mentioned as a contra-indication to treatment.
Side-effects	- Most side-effects are manageable – sometimes by treating them and in other times through dose adjustments. - Severe side-effects drive decisions to terminate treatment. - Side-effects (as a result of already having taken the treatment, or perception of the treatment) are cited as a common reason for patient refusal of treatment. - Some of the same factors can be either comorbidities or side-effects which occur as a result of treatment. - Interviewees cited examples, such as haematological side-effects (e.g. anaemia and neutropaenia), psychosis, skin-reactions, thyroid conditions and ophthalmological indications, dermatological side-effects neuralgia, asthenia, depression and sleep disorders, as important considerations.
Special population groups: age, gender, socioeconomic status, migrants	- Age is an important factor influencing treatment decisions, with older patients less likely to be treated. However, the evidence around what age is considered too old to treat ranges from 65 to 80. Migrants can be difficult to reach with complicated follow-up; in Spain, illegal immigrants don't have access to the healthcare system. - Lifestyle has an important influence on ability to follow treatment. - Gender did not appear to be an important factor, but one UK respondent noted that there were better health outcomes from treatment for women than men.
Behaviour: substance misuse, mental health and prison inmates	- Important behavioural factors include alcohol and substance misuse and mental-health-related behaviour. - Behavioural factors are a very important consideration in decisionmaking about treatment initiation, because of issues such as adherence and prospects for positive health outcomes. - Challenges were explored in treating these groups of people. For example, physicians don't always know how to deal with special population groups (sometimes through lack of experience of dealing with such patients).

[16] Where comments are not linked to a specific country these concepts were relevant across all countries under study.

Table 4.2 Key insights from key informant interviews of health system factors that influence decisionmaking about HCV treatment

Factors influencing treatment decisions	Interview analysis[17]
Referral pathways and decisionmaking across treatment life cycle, access to care and care quality factors	- The decision to initiate treatment is the most complex one; thereafter decisions about dosage adjustments or termination are more straightforward. - Decisions about dosage adjustments or termination are influenced strongly by clinical factors (such as blood test results, side-effects) continued substance misuse and non-response. - The uptake of treatment and quality of HCV care will change once new treatments become available, not least given challenges related to treatment administration as the new treatments will be less aggressive and with fewer side-effects. - In addition to healthcare professional training, patient education programmes are important.but limited by staff shortages.
The relationship between diagnosis and treatment	- Better diagnosis would improve the likelihood of treatment being administered when needed but not necessarily lead to dramatically better health outcomes at the individual level until new treatments are introduced (e.g. due to side-effects). - There would be financial implications on health systems of an increase in diagnosis, particularly with the current treatments, which are very resource intensive to administer.
Organisation of healthcare system: government support and funding	- The economic context is a source of concern in the four countries and physicians worry that decreasing funding will limit access to treatment, and that clinicians will need to "prioritise" patients. - Different levels of support were relayed from the interviewees regarding the level of support from the regional and national government in their country.
Adherence to guidelines	- The perceived level of adherence varied between countries. Spain and Italy felt that adherence to national guidelines was good, whereas the evidence in France and the UK was mixed. - A need for up-to-date and flexible guidelines in Spain was raised.

4.1 The influence of clinical factors on decisionmaking

4.1.1 Viral genotype

Across countries viral genotype was recognised as a factor influencing the nature of the treatment and treatment decisions. In France, a physician mentioned the limited treatment opportunities for patients with genotype 2 and 3 patients who do not respond to standard treatment, as there are no alternatives to offer: "We just wait for the next treatment, hoping that they won't be dead by then (14)."

4.1.2 Haematological abnormalities (including thrombocytopenia (TCP), anaemia, neutropenia)

France

As defined in the standards of care, monitoring of low platelet counts is important and takes place widely. Haematological factors are an important factor in decisionmaking, but it is rare that they are seen as a cause of treatment cessation. For example, when anaemia is a side-effect of treatment, erythropoietin (EPO) is used to boost red blood cells.[18] Specialised centres use neupogen for increasing white cell counts. According to French interviewees, leukopenia or TCP rarely force them to modify or stop treatment but views on the importance of TCP as a factor for treatment decisionmaking are mixed. According to one interviewee, it used to be more of an issue in the past than today, and especially in

[17] Where comments are not linked to a specific country these concepts were relevant across all countries under study.

[18] France is the only country under study where EPO is commonly used for treatment of anaemia.

HIV patients: "TCP is not really an issue. I don't even remember it happened [to such an extent that we had to stop treatment]" (11). By contrast, another said:

> I have two patients who had a severe thrombopenia [sic] (<5,000 platelet per microlitre of blood) under treatment, and I would have liked to use eltrombopag but at the time it was not available. One of my patients died while I could have saved her with eltrombopag. I don't understand why the treatments for thrombopenia don't come out quicker (14).

Two interviewees spontaneously mentioned eltrombopag as a potential solution for low platelet counts issues (14, 13).

Italy

In Italy, as in France, haematological factors are considered important for treatment decisions. Of particular mention were anaemia and TCP. Low platelet counts are carefully monitored, but evidence on thresholds for treatment is inconclusive. According to one interviewee, some centres are stricter than others and won't treat patients with numbers of platelets under 100,000 per microlitre of blood. But others treat patients with lower counts (7). One interviewee felt that thresholds are too high, excluding too many patients who are most in need from treatment for this reason (8).

Spain

As in France and Italy, haematological abnormalities are an important factor in decisionmaking, but rarely induce treatment cessation. Rather, they often determined the dosage given to the patient. However, severe TCP can lead to treatment cessation (16, 20).

United Kingdom

Interviewees widely felt that haematological factors were important in decisionmaking about treatment initiation, adjustment and termination. Most interviewees noted that careful monitoring of platelet counts was mandatory at regular intervals throughout treatment (1, 3, 4, 5) and that guidelines on this topic were very clear, but the extent to which they are adhered to less so (1, 4, 5). As one interviewee pointed out:

> Guidelines for treatment have very strict set points at which treatment with interferon is not indicated. I suspect that most physicians experienced or not are prepared to treat patients with platelet counts that are much lower than 90 or 100,000, which is the specified guideline for PR50A and PR50B (1).

Another interviewee commented in similar light:

> There are clear guidelines. Unfortunately the guidelines chicken out when it comes to the real world and there are many patients who, as they start the treatment, have platelet counts that are borderline on the guidelines anyway (4).

Despite the importance of monitoring haematological conditions at individual level, one interviewee noted that low platelet numbers were relatively uncommon, and hence – in their view – not a major influence on overall treatment dynamics at the level of the wider system (2). This interviewee found that the most common factor influencing frequency of occurrence was low haemoglobin, followed by low neutrophil counts and then low platelet counts.

4.1.3 Comorbidities and related conditions

A number of related conditions influence outcomes of HCV treatment decisions. In our literature review, we identified factors including depression, HIV, HBV, coronary disease,

cirrhosis, non-HCV-related liver disease, diabetes, weight, renal disorders, depression, epilepsy, uncontrolled autoimmune diseases and pregnancy. Interviewees were asked about these and other factors which they felt were relevant.

France

All French interviewees felt that comorbidities were essential to consider. In particular they highlighted the impact of co-infection with HIV, but noted that evidence of the way this impacts on treatment decisions is ambiguous. According to one interviewee, infectious disease specialists treat both HCV and HIV, but they tend to not prioritise HCV because of fears that HCV treatment side-effects will exacerbate HIV, which is often prioritised as the "real problem" (12). There may also be disciplinary power-hierarchies at play (e.g. with HIV specialists at times feeling superior to HCV specialists): "The infectious disease specialist thinks that he's beaten AIDS, that he knows better than anyone, that all HIV patients belong to him… But I think he could do better, and that he could be a better partner"(12). However, another interviewee spoke of very good collaboration (14).

Other comorbidities that were highlighted by French interviewees included HBV, coronary disease (in which collaboration with a cardiologist was identified as important) and immunological diseases in general (not only HIV). Pregnancy was also an important consideration in decisionmaking, because Ribavarin is contraindicated. One interviewee insisted that some comorbidities such as obesity and risky behaviours such as alcohol and tobacco consumption should be controlled during the treatment (15).

Italy

As per France, comorbidities were recognised as important influences on treatment decisions for patients with HCV in Italy. Italian interviewees mentioned HIV, HBV, diabetes, renal disorders, depression (9) and obesity as important comorbidities. One interviewee highlighted the importance of educational programmes aimed at behavioural change for obese patients (6).

Spain

Comorbidities are also an important factor in HCV treatment decisions in Spain. The comorbidities highlighted by interviewees were decompensated cirrhosis, patients on dialysis or with creatinine clearance <50 mL/min, autoimmune hepatitis, uncontrolled thyroid disease, severe heart or coronary disease, sarcoidosis, hemoglobinopathies and pregnancy. One interviewee stated that if "a patient has decompensated cirrhosis, he/she will not be treated, that would be the maximum contraindication" (16). Diabetes and obesity are not an absolute contraindication, but the probability of curing the disease decreases. Interviewees agree on the importance of psychological problems (including depression) when considering treatment decisions. HIV is not a contraindication, but this is a criterion that is taken into account before starting HCV treatment (16, 17).

United Kingdom

Comorbidities are an important factor in HCV treatment decisions in the UK, too. Severe depression, HIV, diabetes, renal disorders, cirrhosis, uncontrolled epilepsy, pregnancy and autoimmune diseases were identified as particularly important comorbidities for HCV treatment decisionmaking (1, 4). In the UK, the risks associated with HCV treatment in patients with comorbidities are discussed and considered together with "how bad their liver

disease is", the probabilities of being cured, and the assessment of side-effects, before treatment decisions are reached (4).

4.1.4 Side-effects

Side-effects from HCV treatment are diverse, and we asked interviewees about the importance of both severe and less severe ones[19] as a factor influencing treatment decisions.

France

In France, side-effects influence treatment decisions but cessation generally takes place only in the case of very severe adverse events. Interviewees cited psychosis and depression, skin reactions, thyroid-related effects and ophthalmologic contraindications as some examples of side-effects they have witnessed. Psychological side-effects require serious attention, as they have been related to fatal outcomes (13, 14, 15). Triple therapy can also have adverse effects on the skin, and partnering with dermatologists is one management approach (14, 15). According to one interviewee, triple therapy also increases anaemia issues (14). All interviewees insisted on the importance of side-effect management in relation with the patient's expectations and their capacity to comply with the treatment. One said: "I try to put less and less barriers to treatment whenever I can" (15).

Italy

Italian interviewees highlighted that side-effects can be an important reason behind patient refusal of treatment (e.g. 9). One Italian interviewee highlighted that the quality of care and clinician dedication to patients is an important factor in the management of side-effects (6). Neuralgia, asthenia, psychiatric problems including depression, thyroid problems, sleep disorders, dyspnoea, convulsions and pulmonary diseases were given as examples of side-effects that are dealt with by doctors and patients (6, 9).

Spain

As mentioned by interviewees from other countries, the Spanish interviewees mentioned side-effects as a factor in deciding whether to continue or stop treatment. As in France, it was noted that only the more severe side-effects such as seizures, certain infections, interstitial lung disease and bone marrow aplasia would affect treatment, and cause treatment cessation. As in France, it was recognised that skin rashes require particular attention as they may turn out to be serious adverse events (20).

United Kingdom

Most interviewees emphasised that trade-offs were important to consider in treatment decisionmaking, and that side-effects needed to be discussed with patients, and weighed up against potential for positive health outcomes. Evidence of prior responses to treatment were identified as an important factor in treatment decisions. One interviewee felt that depression, haematological side-effects (e.g. anaemia, neutropenia) and bacterial infections are particularly important considerations, noting that experts have been "given the message

[19] Side-effects include fatigue, depression, irritability, sleeping disorders, skin reactions, dyspnoea, haematological side-effects discussed above, seizures, bacterial infections, autoimmune reactions, interstitial lung disease, neuroretinitis, bone marrow aplasia, idiopathic TCP and psychosis.

by pharmaceutical companies that the anaemia can be managed by Ribavirin and dose reductions" (1).[20]

4.2 The influence of special population groups, socio-demographic factors and user behaviour on decisionmaking

4.2.1 Special population groups: substance misuse, mental health and prison inmates

France

In France, referral pathways can differ between the general population and special population groups – particularly for points of entry. For example, while most of the patients enter the system through their GP or at the occasion of a routine examination, drug and alcohol misusers may be referred to specialist physicians in outpatient secondary care or to hospitals by centres de soins aux personnalités addictives (CSAPAs) or care centre for addicts. In general, drug users only receive treatment if they are also being treated for their addiction – in this context collaboration between health and social care sectors is essential. Cost considerations present a challenge for access to care by prison inmates, because the Ministry of Justice is the decisionmaking authority for this patient group (11, 12). Whereas there are some very committed doctors working with this population group, stigmatisation is a barrier as are challenges related to their length of stay in prison: "You start treatments in prison and this guy you treat is one day out of prison, and the medical team doesn't even know about it. He doesn't have his medical record, nothing; and for continuation, that's an issue" (13).

Italy

According to interview data, there are no particular policies or restrictions to access to care for special population groups in Italy (6), but there are organisations which promote dedicated and well-organised programmes for special population groups such as drug-users, immigrants, alcohol abusers and prisoners. An example is the Servizio per la Tossicodipendenze (SERT), a public assistance programme for drug and alcohol abusers, providing psycho-social help and therapies for drug abusers. Doctors tend first to try to educate patients and motivate them to change lifestyle factors (e.g. alcohol misuse) before initiating treatment (7), as otherwise there are challenges with adherence and follow-up, as well as higher risks of side-effects (6). Hence, there is widespread agreement that the profile of behavioural and lifestyle risk factors of patients is very important factors for treatment decisions. Some evidence of differential attitudes to treatment, due to financial constraints and the need to prioritise treatment, were also conveyed in the interviews: "We must also think of our country's economy: I cannot spend money on an alcoholic patient" (7).

Spain

Most of the Spanish interviewees stated that testing for hepatitis C in populations at risk is fairly widespread in Spain (e.g. among drug users and people with HIV), and that patients groups with risk practices are targeted and that early diagnosis is promoted:

[20] It was not clear if the interviewee agreed with the pharmaceutical companies' message or if he was suggesting that the perception that anaemia can be managed in this way is incorrect.

> In the case of drug users, for example, patients go to a specialised assistance and monitoring centre for detoxification, The first thing they do in these centres is to test for hepatitis C or other hepatitis, and HIV. The same goes for people who are deprived of their liberty. Upon entering prison they get screened.

Interviewees agreed that everybody follows the same referral pathway, although the entry points must differ, e.g. drug user's point of entry might be through a detox clinic, where standard screening is performed for a series of illnesses. Patients need to be in treatment for substance misuse before they can receive treatment for HCV. Prisoners are the exception, as they are diagnosed and treated in penitentiary institutions. Illegal immigrants also have a particular status, as they are not treated because they do not have access to the health system (except for emergencies). One interviewee raised concern about the HIV co-infected population who, according to him, might be treated for HCV less frequently than the general population (16).

United Kingdom

In the UK, there is strong consensus that behavioural factors are important for treatment decisions, in particular the decision to initiate treatment. Referral pathways differ between the general population and special population groups depending on factors such as drug and substance misuse, and comorbidities (1, 2, 4).

All interviewees raised concerns about special population groups (such as injecting drug users and mental health patients) receiving different care from the rest of the population. They related this to factors including variant physician perspectives on the likelihood of treatment success in such groups, resource availability in the health system and occasionally prejudice (1, 4, 5). Our interviews suggest that mental health patients are not always referred or treated because of care workers' judgement that such patients might have other problems that need to be dealt with first, and fears that HCV treatment might exacerbate the psychological condition (1, 2, 3).

In addition to concerns about differential treatment, interviewees recognised the challenges of managing HCV in some special population groups (substance misuse, prison inmates) in reality, and the need for pragmatic considerations and case-by-case decisionmaking to ensure treatment takes place at the right time (e.g. when patients are "in a good place... motivated... other issues sorted out" (4)). One interviewee commented:

> Once you get a patient who is abusing alcohol you're not going to offer them Interferon treatment, it's a waste of time. Those are chaotic, there's no guarantee that they will be adherent to therapy, they could run into problems with their systems, they could run into problems with heroin overdose because of Interferon. I just think that they are a difficult group to treat without the appropriate counselling, capable scientists, the psychologists, the nurse; we just don't have those resources where I work (1).

However, once treatment is initiated, the process of decisionmaking about continuation or termination and dosage adjustments seems to be consistent across different groups:

> The decisions to terminate are entirely on how an individual patient responds to therapy, both medical responses and their psychological responses, so there's no difference in the pathways. Those that have a drug addiction issue we like to get that stabilised and sorted before we start them on treatment so if they're undergoing a period of dose reduction or

dose stabilisation for methadone therapy you tend to get that sorted first before we start them on treatment but that's the only difference between those two groups (4).

4.2.2 Special population groups – other demographic factors: age, gender, socioeconomic status, migrants

France

In France, treating migrants was identified as a challenge, and there are wider issues beyond just treatment, according to one interviewee: "There was a network of illegal migrants self-infecting themselves, because you can't be sent back if you're sick" (14). Policy change has tried to address this – and now illegal migrants receive treatment only if the disease is advanced (at least two years after infection).

Older patients are also less likely to be treated (as in Italy and the UK), with side-effects and impacts on quality of life being mentioned as key reasons (11, 13), and especially given higher chances of comorbidities (e.g. renal and coronary problems (11)).

Finally, interviewees note that socio-economic status affects the treatment decision, as well as the household structure and support system surrounding the patient (13, 14, 15). An interviewee mentioned the importance of professional and personal factors in the decision to initiate treatment: "Treatment is never urgent; we adapt it to the professional and family life of patients" (15). Having dependants was also cited as a factor to take into consideration (13) before initiating treatment, as the side-effects may diminish the capacity of the patient to take care of dependants. Homeless people also represent a big challenge (12, 13) – recently there have been smaller budgets and fewer staff available in social care, threatening health and social care coverage for homeless people. In addition, as one interviewee put it: "You need a fridge to stock your treatment; how do you do that when you are homeless?" (12).

Italy

In Italy, older patients are also considered a special population group in the HCV field. One interviewee commented: "I wouldn't start a therapy with an active alcoholic patient nor with somebody older than 65" (7). However, the interviewee also emphasised the need to consider the patients biological conditions – hence one factor alone, such as age, needs to be considered in a wider context. Two other interviewees confirmed that patients over 70 are generally not treated (8, 9). An interviewee identified challenges with immigrants, specifically related to reliability during treatment (e.g. they don't come to follow-up consultations). Evidence from the Italian interviewees suggests that socioeconomic status does not influence treatment decisions and access to care. However, Italian interviewees identified ethnicity to be an influencing factor on treatment outcomes (of Afro-Americans) – although not necessarily treatment decisions (6).

Spain

In Spain interviewees mostly mentioned socio-economic factors as a proxy for the capacity to understand and follow the HCV treatment (17, 20). One interviewee also referred to the importance of the social and family support available to patients, as well as the psychological and social resources they can benefit from (16).

Age *per se* was not seen as a factor influencing decisionmaking, but was taken into consideration in decisions about treatment in conjunction with other factors such as stage

of disease (17, 18, 20). However, age can still be a barrier to treatment as it tends to be correlated with knowledge and awareness: "Young generations tend to be more informed than older people" (18).

United Kingdom

In contrast to the quasi consensus about substance misuse, prison inmates and mental health patients, there were mixed responses about the importance of demographic factors such as age, gender, ethnicity, socioeconomic status and migration status. Some physicians said that they were not so important (2, 3) while others said that gender and age actually do impact on treatment decisions (1, 4) – views included that "if patients are 80" and have mild disease they do not need to be treated, and that the older the person is the less likely the treatment is to cure them (1). Most people felt that gender is not important in the treatment decision, but one interviewee emphasised that it is a clinician's responsibility to "make the patient aware that you know if they're male they've got a lower chance of a cure than a female" (4). According to one interviewee, migrant status matters as migrants tend to have different expectations of care and a poorer understanding and awareness of the treatments (4).

4.3 Health system factors influencing HCV treatment

As identified in the literature review, the organisation of the health care system can have an important impact on decisionmaking about treatment for HCV. This was even more evident in the interviews than in the literature review.

4.3.1 General features – referral pathways and decisionmaking across treatment life cycle, access to care and care quality

France

Referrals and decisionmaking: In more than 60% of the cases in France, HCV is diagnosed because of an exam for anaesthesia, a surgery, or a check-up as part of routine testing associated with other conditions. GPs are responsible for most of the referrals to secondary care. After a first (incomplete) diagnostic, they refer patients to a hospital or an outpatient hepato-gastroenterologist (where there is a shorter waiting time) for a full diagnostic. The outpatient hepato-gastroenterologist may then decide to send the patient to an infectious disease or hepatology department in a hospital, or a reference centre for the region (usually part of a big university hospital), if the patient's case is complicated. The particularity of the French system, where secondary care specialists can be accessed without referral from a GP, makes it also possible to have an initial specialist consultation following the recommendation of a friend or a pharmacist (15).

According to interviewees, half of the diagnosed HCV cases in France don't need treatment, but patients still need to be monitored, generally by GPs. If monitoring doesn't take place effectively (and this is an issue for the system (11, 12)), then patients are lost from the follow-up. Nurses tend to be responsible for patient education, but because of severe nurse shortages (12, 14), this often falls to doctors in hospitals or outpatient specialists. Patient associations are also involved in education, but are not equally well represented across the country – for example patient associations are less prominent in the

south east of France (14), while in the reference centre in Lyon patient associations work very closely with clinicians (12).

The decision to initiate treatment is complex – in general, the more advanced the disease progression is, the more heavily treatment is recommended. Reported barriers to initiation in France include:

- key findings on factors influencing treatment decisions (e.g. their diversity, contraindications and co-morbidites
- patient refusal of treatment because of duration and administration requirements and side-effects
- clinician decisions not to initiate treatment at their discretion
- age-related barriers (with age all the previous factors become even more important).

Common causes for treatment cessation tend to be unresponsiveness (e.g. in genotype 2 and 3 patients) and severe adverse events, including psychological events.

Quality of care and patient perception factors: Overall, interviewees felt that the quality of care is among the highest in Europe and relatively standardised across the country, and that France is one of the world leaders in treatment of HCV. This was partially explained to be the result of all the efforts that have been made to compensate the "original sin" of the contaminated blood scandal – according to one interviewee high treatment availability tries to partially compensate for the fact that victims of contaminated blood products were not financially compensated (12). One interviewee noted that "there are more outpatient specialists than in Germany or Italy" [independent but publically funded] and so the entire system doesn't depend solely on hospital trusts (as it is according to him the case in the UK, Germany, Spain and Italy (12)). There was strong consensus that the quality of treatment and treatment outcomes will improve tremendously in the next three to four years, when the next generation of drugs is available. It was mentioned that France immediately treats 16% of diagnosed patients, compared with approximately 5% in Sweden (13), and France is the only country (compared with other European countries and the USA) where the patient can have as many treatments free of charge as needed. In Belgium for instance only the first treatment is free, and treatment access is concerning: "We try to help them, but the situation is so difficult there" (13).

However, some challenges in managing special population groups (substance misuse, homeless people and migrants) do exist. A need for more nurses to provide education for patient and supportive communications was identified by several interviewees (12, 14, 15). Discontinuities in the therapeutic relationship in public hospital settings (at each visit the patient sees a different face: a doctor, a nurse, a psychologist) were also seen as a threat to adherence by one interviewee (15).

Patient perceptions and awareness factors: Interviewees agreed that a patient's motivation is the main barrier or enabler as far as treatment initiation and continuation is concerned. One said, "that is the most important thing" (13). Moreover, engagement with patients is seen as important for treatment outcomes to be successful. One interviewee commented: "You have to prepare [patients]. There have been so many interrupted treatments because patients couldn't stand it. They were not ready, all of this requires support, and means as

well. You need to train a support workforce" (13). Side-effects can be better tolerated if the clinician provides quick answers and reaction in crisis situation: "[To deal with side-effects] you need to be available... to be able to answer a call within 5–6 hours" (15) and to find the words to put the patient at rest.

Italy

Referrals and decisionmaking: Unlike other countries, there are no early diagnosis and screening programmes in Italy, and dialogue with GPs on this matter has not yet led to any changes in practice, hence referrals generally take place quite late. The point of entry is generally a GP practice (9), but for drug users entry can occur through the SERT (7). Soon after the first diagnosis the patient is sent by their GP to a hospital (gastroenterology department) for diagnosis confirmation and treatment. Most interviewees emphasised the importance of educating patients and follow-up. The diagnosis stage is the most complex, and thereafter the Italian system is – according to interviewees – relatively efficient. However, the arrival of new and more complex treatments will require some changes in the organisation of the care system with the emergence of highly specialised centres able to deliver those treatments (7).

A modification of treatment is mandatory in the case of side-effects or toxic effects caused by a drug (6). One interviewee thought that decisions to adjust dosage or terminate treatment are also possibly influenced by predictive clinical factors such as genotype, interleukin 28B gene and HCV RNA.

Quality of care and patient perception factors: Although interviewees' views on the quality of care were mixed, there was a general view that specialists and nurses are well trained, but that issues in care quality were a result of staff shortages, that more doctors and hospital staff would provide better patient care and management of the disease, and that there was a need to minimise bureaucracy. One interviewee noted that the quality of care varies across centres and depends on the doctors' commitment (8); another said that quality varied across the country with the north benefiting from much better services (10); while another noted they had never heard of a bad experience or patient complaint at their centre (9).

Spain

Referrals and decisionmaking: Detection or diagnosis usually occurs in primary care (family doctors, work centres, annual check-ups at the workplace). From primary care, patients are referred to a specialist in outpatient care. However, if the specialist thinks a patient needs to be treated or if a biopsy is needed to quantify the severity of the disease, the patient is referred to a hospital (18, 20). Treatment and prescriptions tend to take place in the hospital (18, 19, 20). Drug users may be referred by a specialised assistance and monitoring centre for detoxification rather than by a GP. As in France, inmates are treated in a different system: prisoners are under the responsibility of the Ministry of the Interior, though public health services have certain agreements with the ministries to provide diagnostic and treatment services (17).

The decision to initiate treatment is based on the stage of the disease (19, 20), and on whether the patient has been treated before or not. When a patient has not responded positively to a drug, doctors might think about whether to continue treatment or wait until the next "generation" of drugs enter the market (16). "Because a naive patient does not know what the side-effects are, so he/she will probably say 'yes, I will do it'. But then

when the side-effects of the drugs start the patient says: 'what did I get myself into?'" It is to be noted as well that treatment decisions are not standardised across the country and that the autonomy of the regions allows for great variation (16).

Quality of care: Interviewees observed that physician experience is important in determining the quality of care received, and one interviewee stated that the experience of the physician in treating HCV patients with HIV was particularly important for that patient group (16). One interviewee noted that the role of nurses was very important, but that unfortunately hospitals are increasingly reducing their role in favour of doctors (18).

Patient perceptions and awareness factors: Interviewees stated that physicians always took into consideration whether they felt that the patient would be compliant to the treatment when making their decisions about whether to treat or not:

> The patient profile greatly affects decisions on whether to treat a patient. If, for example, a doctor has the perception that a patient will not be able to continue treatment because she/he lives in semi-exclusion or exclusion, injects drugs, or otherwise the physician will probably not offer the treatment; likewise, if a patient is not sufficiently informed or cannot self-manage his/her health (19).

United Kingdom:

Referrals and decisionmaking: According to most interviewees, UK patients tend to be referred from primary care, without a full diagnosis. However, one interviewee pointed out that detection generally takes place in specialist care, in hepatology clinics (5). Following diagnosis, patients tend to be referred to specialist centres in hospitals for genotyping and treatment decisions. Although, according to one interviewee, there is no "one size fits all" pathway, day-to-day decisionmaking on treatment generally takes place at the clinician level, and the patient pathway involves a diverse set of professionals including clinical nurse specialists, physicians, hepatologists, infectious disease physicians and clinical virologists.

The decision to initiate treatment is a complex one, and views on who influences the decisionmaking process and how vary:

> It [treatment decision] depends on whether they're men or working. It depends on their age. It depends on how long they have been infected for and it depends on the degree of cirrhosis they have and their viral load, and it depends on their gender. So all of those factors predict the likelihood of cure and then if they have an alcohol problem or a significant drug problem that to an extent dictates how easy or hard it's going to be for them to procure the therapy, although our experience is that you know they do very well and that we're not seeing a difference between them and the general population (4).

According to one interviewee, although patients are involved, ultimately they rely on the clinician to make the judgement (2). By contrast, another interviewee said it is the patient who ultimately decides, following a standard education programme for patients (4). A third interviewee emphasised that nurses influence clinicians' day-to-day decisions (5). One of the biggest challenges, according to one interviewee, "is who should be treated now or who should wait for treatment, and I think that's a very individual decision and varies from centre to centre and person to person" (1). Interviewees agreed that once treatment is initiated the subsequent decisionmaking about dosage adjustments and/or termination are more standardised, and the guidelines generally clear and followed by clinicians. Blood

results are a key influence (4) on these decisions, including platelet counts, haemoglobin, and neutrophils. As one interviewee put it:

> for example if you have quite clear markers of, you know side-effects that are easy to judge, like for example if your platelets fall to a certain level, if your haemoglobin falls to a certain level, if your neutrophils fall to a certain level. It's those three things to potentially really watch that are likely to lead to dose reduction. And, you know, I guess if somebody's lifestyle is such that they simply can't follow the regime then it will be stopped just because it's a waste of money (2).

In addition to blood test results, dose reduction and discontinuation decisions are often associated with side-effects and serious adverse events (1, 2, 5), and occasionally continued substance misuse. Although clinicians generally make such decisions, patients sometimes discontinue treatment themselves (1). Evidence from interviews is mixed on the types of clinicians responsible for decisionmaking about adaptations or termination of treatment. For example, one interviewee said that nurses often decide on dose reduction (1) but another emphasised that nurses cannot make decisions about commencement or discontinuation without reference to a specialist consultant (2).

Quality of care: Interviewees identified that physician experience has an important influence on the quality of care patients receive, determined in part by the number of patients they see. A lack of experience in prescribing was said to complicate adherence to guidelines and the uptake of available treatments (1, 2, 4, 5). According to one interviewee, the uptake of treatment and quality of HCV care will change once new treatments become available, not least given current challenges related to treatment administration (cold storage needed for injections), and prospects for new treatments being less aggressive and with fewer side-effects: "I think that GPs should be made more aware that we're opening a window to new treatments but the big bang is really going to come when you get free of Interferon" (1). In general, the quality of care was seen to be more consistent across Scotland and much more variable in England.

Patient perceptions and awareness factors: Interviewees had mixed views on how important patient perceptions of the quality of care were for treatment decisions and treatment outcomes (e.g. ratings of service provider, patient experience, patient awareness, waiting times, dignity and respect). Some felt it is not so important because of equal quality of care across the region (in Scotland) (3), and others that it is very important and influences the patient ability or willingness to follow the course of treatment (4). One interviewee emphasised that support from high quality nurses can make a huge difference (2). Another said:

> The patients don't have a choice. They're either with us or they're not with us. It's very much a team effort between us and them to try and get them through treatment. So getting that perception is very important early on because adherence to therapy is vital to success and unless they're you know clearly signed up and on board and with you they're not going to work with you to get themselves through treatment (4).

4.3.2 The relationship between diagnosis and treatment

France

Approximately one-third of the infected population is estimated to be undiagnosed. Some patient groups advocate for more population-wide screening, but according to one

interviewee it is better to target screening, and not incorporate additional or more screening in the general population overall (11). There was general consensus among interviewees that major improvements in detection have been realised over the past few years. Most felt that further improvements in diagnosis could be managed by the healthcare system; although they highlighted that there would be implications on financial support needed in the universal coverage model, as well as challenges related to longer waiting times. Interviewees also emphasised that new treatments (triple therapy) are particularly challenging to manage and administer, exacerbating waiting time issues and challenges related to side-effects. Workforce issues could also pose a growing challenge if a higher number of individuals were diagnosed and needed treatment, especially new treatments.

Italy

Under-diagnosis is a big challenge in Italy (one interviewee noted that it was a particular problem in Southern Italy), in part due to a lack of screening programmes because of financial constraints (8).

Additional challenges also include bureaucratic issues, such as the slowness of laboratories in providing test results (6, 7), and the lack of appropriate patient awareness and education programmes to minimise risks of contracting the disease or of side-effects and adverse events during treatment (9). Interviewees did not report any major changes over time in the detection, testing and treatment of the disease, but some expressed views about the need for specialisation and organisational stratification according to patient needs. Similar to some French colleagues, Italian interviewees emphasised that there would be cost implications to the health system from improvements in diagnosis rates, and that new therapies may also pose financial challenges for the Italian system.

Spain

There was a consensus among Spanish interviewees that HCV is not considered a priority by the policymakers and that a large proportion of the infected population are not diagnosed. According to one of them, they estimate that in the Valencia region 1.5% of the population is infected, while only 16% of the infected population is diagnosed (17). Under-diagnosis is identified as both a barrier to treatment and a challenge to cost-effectiveness (20). Interviewees felt that this barrier was not currently being addressed through strategies such as awareness campaigns. However, it seems that high-risk groups benefit from better screening than other patients (16, 17). There have been changes in the past year after the arrival of new drugs, and a change in the guidelines as a result of the new drugs. Increased diagnosis would lead to an increased challenge of lack of economic resource in the regions as well as at national level. This is a particular problem with new treatments as they are more expensive than existing ones. Treatment is becoming more personalised, and one interviewee said that the arrival of these new drugs has stimulated the detection of new cases with more information about them in the news (19).

United Kingdom

There was strong consensus between the UK interviewees that under-diagnosis was a significant barrier to treatment, but also recognition of growing awareness about the disease (1, 4, 5). In Scotland, diagnosis rates have improved due to the Action Plan (Scottish Government, 2006), of which phase 1 was implemented in 2006 with a huge

investment of money into hepatitis C (1, 3, 4), and according to one interviewee, 60% of the infected population is diagnosed, and 25–30% of the diagnosed population on treatment within a year (4). Particular ethnic groups (e.g. Pakistani) and special population groups (such as drug and alcohol mis-users) are more difficult to reach and therefore to diagnose (1, 2, 5), and there are some outreach services for such groups (4). The process of detection and treatment has improved over time for both the general population and high risk groups, and one interviewee noted that this was the case especially regarding adherence to guidelines (2). In part, improvements in England were attributed to a big push and campaigns to change physician attitudes and peer to peer education for patients about diagnosis and treatment (2).

Although better diagnosis would, at a system level, improve the likelihood of treatment being administered when needed, some interviewees said that improved diagnosis would not necessarily improve health outcomes for patients dramatically until new treatments were available (3), that side-effects would still be a barrier in this regard, and that there would be new demands on financial resources and the healthcare workforce (e.g. monitoring them) (2). The complex nature of the current standard of care and associated high human resource costs raise questions about how higher demands for treatment would be financed, although there is a need to better understand the cost economics for health systems over the long term, including cost–benefit trade-offs (1, 2, 4, 5). In the shorter term, there could be health financing challenges, as one interviewee pointed out: "The Scottish Government has said that no one will be denied treatment. I think that would give them a huge headache if we were that successful that quickly and... their words would then you know come back to haunt them" (4).

4.3.3 Organisation of healthcare system: government support and funding

France

Overall, interviewees felt that government attention to HCV was appropriate with individual experts on hepatitis being represented in key policy bodies. As one interviewee noted, there is usually a "Mr Hepatitis" within the Ministry of Health and the Health General Directorate[21] (12). Also at the national level, the Institut de veille sanitaire (Institute for Public Health Surveillance) was seen to be doing a very good job on the epidemiology front, but according to one interviewee, INvS has concerns about the costs of treatment and the financial implications of advocacy for new screening campaigns by bodies such as SOS Hepatitis (a patient association).

Interviewees did not see cost to be a major barrier for HCV treatment in France at the system level (beyond general funding and staffing issues in the French healthcare system, which are not HCV disease specific, such as nurse capacity). Hospital and outpatient services are free of charge. However, there were some concerns about rising costs associated with new treatments – according to one interviewee, hospitals in Lyon are facing bankruptcy and new, more expensive HCV treatments are creating tensions in the system, "so the patient ends up stuck in the traffic jam or waiting list, as in England" (12).

[21] This is a directorate within the ministry. There are other health directorates such as for example the Centre for Health Care Supply

Interviewees also commented that research funding for HCV is in competition for funding for HIV, as the budget rests within the same institution (National Agency for HIV Research). According to one interviewee, 80% of funding goes to HIV because HIV associations are much more vocal, even though HCV kills 20 times more people each year (13).

Italy

At the moment there is no direct or indirect prioritisation of HCV as a disease area by policymakers in Italy. One interviewee felt that policymakers tended to underestimate the impact of the pathology, which is considered a chronic disease among others (10). There is still a stigma towards people affected and advocacy is still limited (10). Prioritisation takes place within clinical settings (given needs to manage limited budgets), and one interviewee emphasised that "economical reasons have a strong impact on a doctor's decision" (8), suggesting that rationing may apply. Evidence on how this might influence equitable access to therapy is inconclusive, however. According to one interviewee, less urgent therapies are sometimes postponed because of financial challenges and staffing constraints (8), while another said that the funding model had no impact on access to therapy (7). The private healthcare sector does not tend to focus on HCV, and according to one interviewee public centres are relatively well organised and do not have long waiting lists (9), so most HCV patients rely on the public sector.

Spain

A number of interviewees mentioned that policymakers were not keen on hearing about HCV or increasing diagnosis as this would mean that more patients would need to be treated, which is costly. The cost of HCV treatment is put forward as a reason for the lack of political commitment (19, 20), and one interviewee said that policymakers do not even support awareness campaign developed by patients associations (16). As a consequence, people are misinformed (20).

Treatment is offered at a public sector level and usually guarantees universal coverage (17). However, the current economic crisis has had a strong impact on HCV treatment (18). Similar to other countries, the arrival of new and more expensive treatment (triple therapy) is seen as problematic, especially because currently the criterion of cost is already prevailing in all decisions (17).

Moreover, differences exist between regions (autonomous communities). Each region can decide what medicines and how much funding will be available to treat HCV. Hence there is inequality in access to public health treatments: "The situation in Spain is so surreal that depending on the autonomous community in which you live, you'll have access [to] drugs for hepatitis C or not" (16).

United Kingdom

Interviews suggest that there is regional diversity in the levels of priority and resources invested into HCV as a field by policymakers in the UK. For example, there is greater support for HCV patients available in Scotland than England. According to one interviewee, intense awareness raising and advocacy campaigns influenced the development of an action plan in Scotland in 2006, supported by £43 million investment (4). Within England, the level of government attention to HCV and scale of investment varies across region, and views on the appropriateness of the current levels of investment varied across

interviewees. For example, one interviewee commented that although there is a lack of ring-fenced funding, the budget is overall appropriate for needs, although additional support for the funding of first generation protease inhibitor treatments would be beneficial (1). Another emphasised that the levels of funding ring-fenced for hepatitis C were "a postcode lottery" (5). The fragmented landscape view was also emphasised by another interviewee, who pointed out that Manchester is the only region following a similar approach to Scotland (centralisation), and that in the rest of England government support on HCV is more akin to "the less good parts of the world where there isn't a systematic approach but dependent on one or two champions in larger teaching hospitals to take the club and go with it" (4). However, apart from the level of funding, the funding model in the UK being NHS based meant that an important question was whether the NHS was "going to impose on us a particular blend of patients or put a cap on the numbers because there's no new money in the kitty, and we don't know that yet and we're busy finding it out" (1).

4.3.4 Adherence to guidelines

France

Although national guidelines are clear, evidence on adherence to guidelines is mixed. One interviewee was sceptical as to whether GPs test for HCV as much as they should – especially in the case of some challenging special population groups, and about the extent to which prison inmates who simultaneously use drugs benefit from HCV testing according to guidelines (11). Another interviewee acknowledged that guidelines for treating drug addicts are probably not always followed, given difficulties in follow up and chances of successful outcomes (14): "There are several discrepancies... but we try to stick to them" (14). EASL guidelines are used as a reference,[22] including for areas where France does not yet have guidelines (e.g. triple therapy). Interviewees found that biggest challenges to adherence apply to decisions about when to initiate treatment: "The difficulty is when do you treat? Some wait too much, while the threshold is very clear" (12). This is often due to patients' and clinicians' fears of side-effects.

Italy

According to Italian interviewees, adherence to national and EU guidelines is good across the country; although one interviewee mentioned that Italians tend to be "more flexible" with regard to guidelines than physicians from other countries (6) There are no major challenges to understanding of or adherence to guidelines at present, but the introduction of new therapies could make adherence more complicated, as specialisation of care will increase and new centres may not be available across the whole country (7). According to interviewees, adherence to formal hospital procedures is followed widely.

Spain

Most Spanish interviewees stated that adherence to national guidelines is good. One of the reasons given for this is that "it includes an algorithm that classifies patients based on a profile and indicates when patients should be treated and when they should wait. The Spanish Agency of Medicines has developed these protocols with input from important hepatologists and scientific societies" (16). However, one interviewee noted that these

[22] They are very similar to French Consensus Conference 2002 guidelines, but more up to date.

protocols are too inflexible. "Guidelines are too inflexible: they do not conform to the complexity of human beings, there are many things you need to take into account when treating/monitoring a patient" (18). The same interviewee also regretted that guidelines tend to recommend delay in the treatment (to not treat people who are at the early stage of the disease). Another interviewee stated that good guidelines existed, but they are not always followed because of economic constraints (20). There is some concern about whether guidelines are up to date. One interviewee stated that the guidelines for diagnosis were out of date. When comparing national guidelines with EASL, they are seen to be quite similar with regards to the treatment, but differ when it comes to diagnosis.

United Kingdom

Evidence on adherence to guidelines is ambiguous, but there was general agreement that adherence to guidelines has improved over time. Moreover, some interviewees felt that adherence to guidelines for treatment initiation decisions were variable across the country. The main identified challenges to guideline adherence were: patient adherence (especially in the case of difficult side-effects) (1); lack of physician experience in prescribing, associated with how many patients and what types of patients they see (1, 2, 5); challenging administration (injection, cold storage) influencing, in particular, the drug-using population (1); clinician perceptions about likelihood of successful treatment in special population groups; and financial resource constraints (5). Overall, guidelines on adjusting dosage or terminating treatment tend to be more standardised across patient profiles (and better adhered to) than guidelines about decisions to initiate treatment, which is not surprising given the higher complexity of the initiation decision. Guidelines are clearer for new direct-acting antivirals (interferon and ribavirin) than previous treatment approaches, but there is scope for improvement in areas such as dealing with special population groups, e.g. mental health patients.

We did not gain much evidence about other aspects of regulation such as standards and drug approval; drugs in Scotland need to be approved by the Scottish Medicines Consortium, and one interviewee said that the UK follows European Medicines Agency prescribing guidelines (1). National comparative standards are needed and there is a hope that there will be improvement in this regard within a year or two of using new agents (1).

4.3.5 International comparisons of treatment practices

Table 4.3 provides views of interviewees on practice in countries other than their own.

Table 4.3 Views of country experts on international comparisons

Views of French interviewees	Views of Italian interviewees	Views of Spanish interviewees	Views of UK interviewees
- There was strong consensus among interviewees that they have an exemplar system, especially compared with other European countries - In France, there are more specialist physicians treating HCV outside the hospital than in Germany or Italy. This is particularly true for the south east (12) - In England, Germany, Spain and Italy, the whole process revolves around university hospital trusts (12) - France is the only country where the user can have for free as many treatments as needed. In Belgium, for instance, the first treatment is free, but that's all. Germany and Canada were mentioned as nations which were behind France (13) - France is very good at treating HCV because of all the efforts that have been made to compensate for the "original sin" of the contaminated blood scandal. Availability of treatment tries to compensate for the fact that victims of contaminated blood products were not financially compensated (12) - In France 16% of persons diagnosed are treated immediately; in Sweden or in the UK, the figure is 5% (13) - France is the only country commonly using EPO for anaemia (11, 14)	- Few details on international comparison were provided – the interviewees suggest that practice is similar to other countries - However, one interviewee noted that Italians are sometimes less strict than some other countries in applying the stopping rule: "we are Italians... less severe and more flexible" (6) - There are differences in the way reimbursement is dealt with compared with the US system. According to one interviewee, there is a higher need for prioritisation than in the US where treatment is paid for by insurance (6)	- Differences are mainly viewed to be at the diagnosis stage, determining the number of patients identified, and therefore the number of patients treated. The more economic difficulties a country may have, the more the diagnosis is limited (18) - Richer countries (like Germany) have the possibility to treat more patients (19) - Countries such as the USA are more flexible when it comes to following guidelines and recommendations (19) - Wales, Scotland and France were given as examples of countries with specific HCV programmes, including screening for high risk population groups (20)	- In Belgium, treatment is only given to people with significant liver damage (2) - France has a much higher level of screening than the UK (2) - The USA is similar to the UK (2) - Bulgaria requested help from Scotland for its action plan (4) - Although France and Germany have a much more open process of treatment, whether the patient can pay or not affects standard of care (4) - It feels as though there is less stigma attached in France, more in the UK, which affects patients' perceptions of treatment etc (4) - One interviewee said that most places were "better" than the UK, in particular Germany and Italy (5) - "To be honest France is probably the most advanced; I think they're probably at about 70% of their prevalent pool they've diagnosed. You know the US is sort of down where we are and that's one of the reasons that their Centre for Disease Control has just proposed that they should screen everyone born between 1945 and 1965" (2) - "I do think that there are people in Scotland who are getting therapy and these are people who'd never get it elsewhere and partly because they couldn't afford it; they'd have to pay for it" (3)

4.4 Conclusions

The interviews constitute a valuable addition to the literature review. When comparing the data from both sources we found no major contradictions in the nature of factors that influence decisionmaking to initiate, adjust and terminate treatment for HCV. In general, interviewees' opinions on the factors affecting decisionmaking were similar across all four countries.

As for clinical factors, it was observed that platelet counts of patients on and off treatment were monitored in all countries, but the evidence for thresholds on when to start, stop or adjust treatment was relatively inconclusive in the real world. In France and Spain, it was noted that it was rare that haematological factors would induce treatment cessation, but rather adjustments in treatment. There were mixed views on the importance of TCP in treatment decisions: in France there was no clear evidence on this and in Spain it was observed that TCP could lead to treatment cessation. Genotype was a strong factor in decisionmaking in all of the countries, as were comorbidities, particularly HIV, depression, diabetes, HBV and cirrhosis. All interviewees noted that there were trade-offs when it came to consideration of side-effects. In France and Spain, it was noted that only severe side-effects would lead to treatment cessation, but in all countries side-effects were a major part of the consideration of whether to initiate, adjust or terminate treatment.

Demographic and behavioural factors played a big part in treatment decisionmaking, mainly in treatment initiation, across all four countries. Most interviewees noted that the decision to initiate treatment was different for special populations (substance misuse, inmates, etc), due to a consideration of challenges of adherence and stigma of HCV for certain health care providers, as well as the referral pathway and entry point. Demographic factors such as age also featured in decisionmaking, although clarity on thresholds was not found, and the consideration of age tends to be in conjunction with other factors. Migrant status also played a role in treatment decisionmaking, because of migrants' limited access to care and education. Interviewees from France and Spain also mentioned socioeconomic status as a factor in decisionmaking, considering the available support structure and awareness and education of patients.

The referral pathway for HCV patients is similar in the countries we studied. In most countries, diagnosis is undertaken at primary care, or incidentally, and then the patient is referred to specialist care. The quality of care seems to vary widely across and within countries (although France was recognised to have higher quality of care than elsewhere), with physician experience with HCV cited as a major factor in determining quality of care. All of the countries noted that with changing treatments, care requirements would also change. Under-diagnosis is still a major problem in all of the countries, although diagnosis levels are increasing in some of them. Most interviewees felt that with an increase in diagnosis would come a constraint on available resources, particularly exacerbated by the arrival of new, more expensive, treatments. There appeared again to be variation in government support and funding across and within countries. Large regional diversity was noted in the UK and Spain, and underfunding was considered a problem in most places. Interestingly, a Spanish interviewee noted that policymakers were not keen to hear about

HCV or increasing diagnosis because of predicted limitations of resources should there be increased diagnosis.

There was ambiguous information about adherence to national and European guidelines on treatment initiation, adjustment and termination, with particular concerns raised about adherence once the new therapies become available.

CHAPTER 5 Mapping patients' journeys for HCV treatment

This stream of work sought to map the different stages HCV patients pass through once they have entered the healthcare system and identify, for each stage, potential points of departure from the typical journey that might be influenced by patient or system-specific factors. While HCV patients typically enter the system through their GP or drug or addiction services, further passage through the system is influenced by factors including the way the care system is organised and financed, the patterns of communication between care levels, responsibilities for management, monitoring and follow-up (or lack thereof), existence and applicability of practice protocols and guidelines, reimbursement mechanisms, scope of clinical decisionmaking, and access to new treatments.

Given the very specific clinical requirements of treating HCV-infection, it is perhaps not surprising that the "typical" HCV patient journey tends to be similar across France, Italy, Spain and the UK. The typical point of entry in each system tends to be primary care, frequently also the location for initial diagnosis. Full diagnosis and confirmation of diagnosis, as well as treatment, is typically provided in secondary care units in hospital or by specialists outside hospital. This chapter provides a brief summary of patients' pathways for treatment in the four countries under study and a discussion of the barriers and gaps along the HCV patient journey.[23]

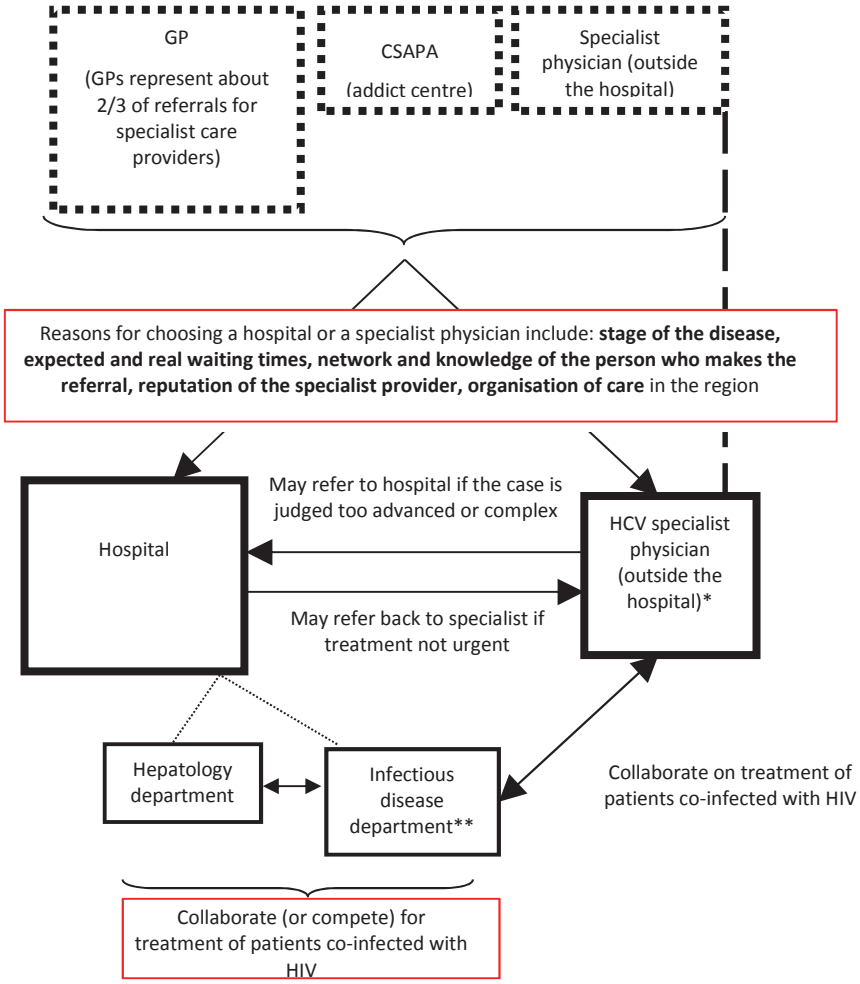
[23] Prison inmates are not included in the analysis for France, Italy and Spain as they are treated in a different system, which is under the authority of the Ministry of Justice.

5.1 France

In France, interviewees gave a rather detailed picture of the "typical" journey for HCV patients, highlighting the nature of the relationship between the different stakeholders, and identifying the main challenges.

The HCV treatment delivery system was also considered to be fast moving, with increasingly more clinicians being able to prescribe HCV drugs.

Figure 5.1 The HCV patient journey: France



NOTE: The fact that referral is not necessarily needed to access specialist care allows another point of entry than the GP.

*The role of specialist physicians outside public hospital is particularly relevant in the dense medical coverage[24] of the South East region.

**Interviewees mentioned infectious disease departments when referring to HIV co-infected patients.

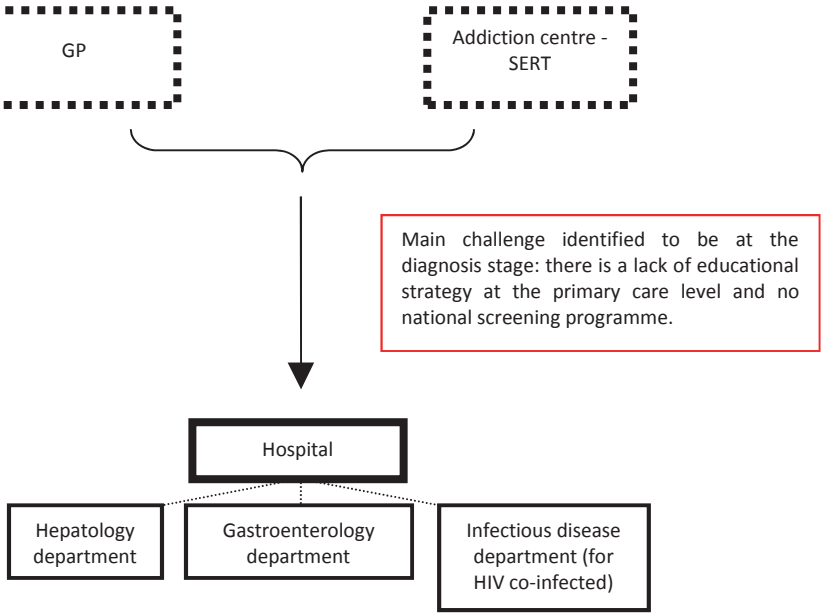
[24] The South East PACA region, including the Côte d'Azur, has one of the highest densities of GP and specialist physicians in France. See Sicart (2011).

5.2 Italy

In Italy, the HCV patient journey begins with the patient entering the system either through the GP or the addiction treatment centre for the initial diagnosis. Confirmation of the diagnosis and subsequent treatment is by referral to hospital specialist departments.

However the patient journey is likely to change, with the emergence of outpatient specialist services and the role that outpatient specialist physicians (hepatologists) are expected to play in prescribing and delivering the new drugs.[25]

Figure 5.2 The HCV patient journey: Italy

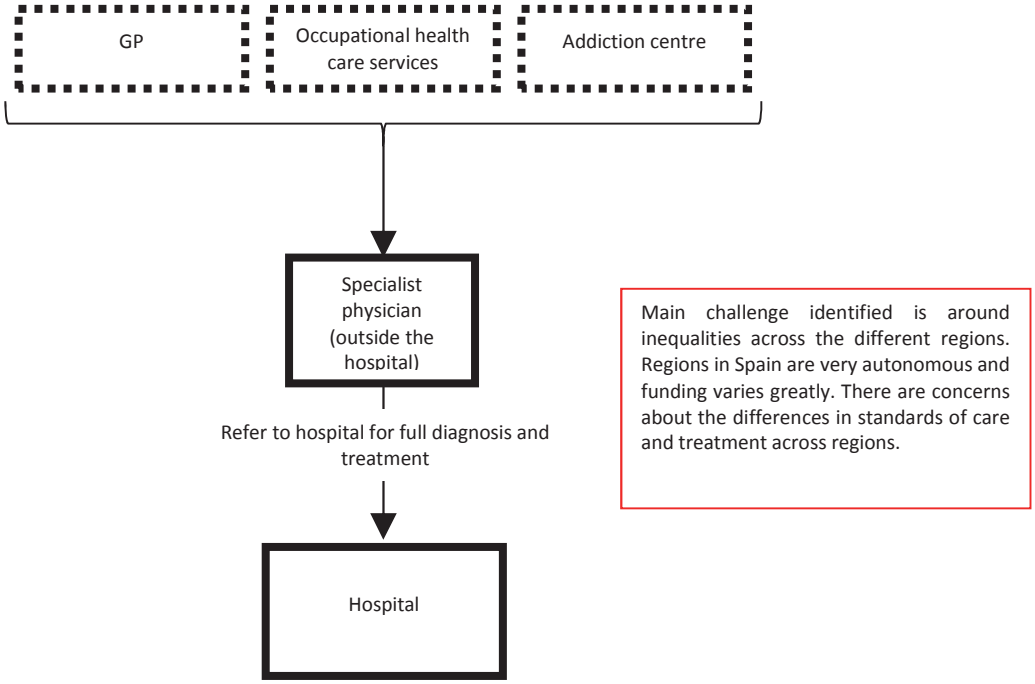


[25] Physicians are likely to have an incentive to prescribe high cost drugs, and may try to keep patients in their services rather than referring them to hospitals.

5.3 Spain

In Spain, there seems to be an additional step in the HCV patient journey: from primary care, the patient is referred to specialist care, before being sent to a hospital for full diagnosis and treatment.

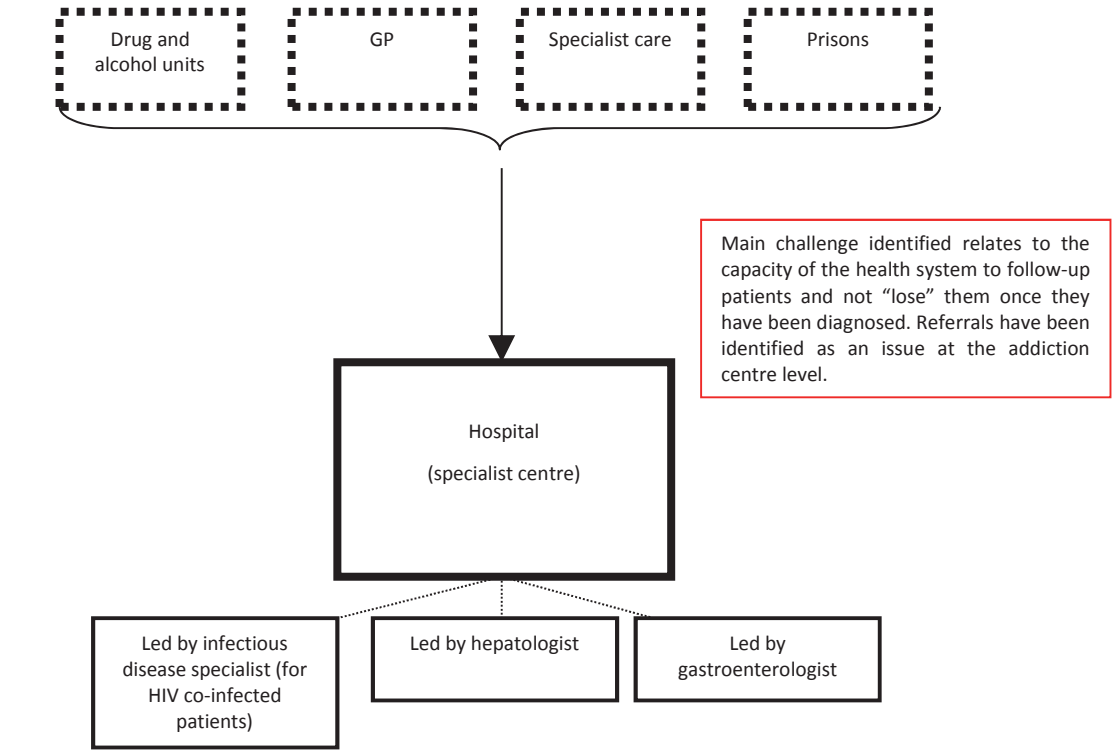
Figure 5.3 The HCV patient journey: Spain



5.4 United Kingdom

Similar to the other countries under study, in the UK people with HCV infection typically enter the system through their GP or a centre for addiction; additional routes include through the prison system and directly via specialist care. In other countries, prisoners seem to be treated in a parallel system (under the authority of the Ministry of Justice in Spain and France).

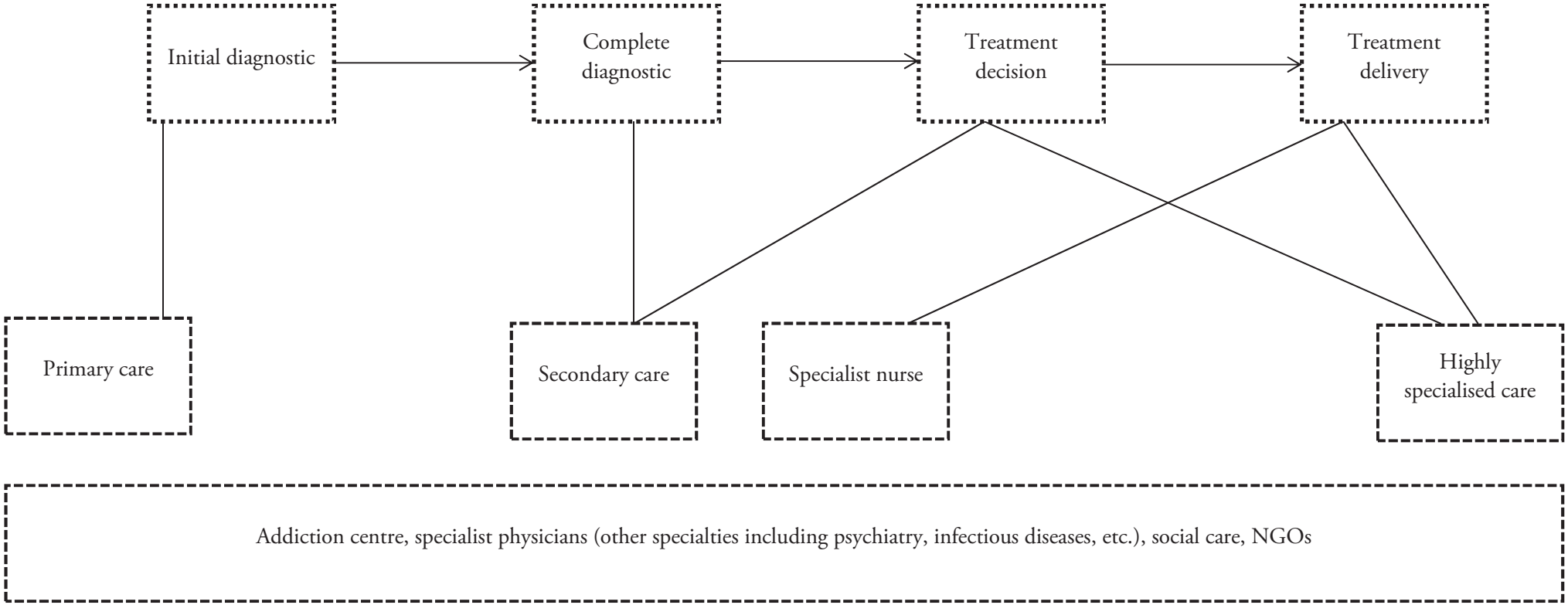
Figure 5.4 The HCV patient journey: the UK



5.5 Barriers and gaps along the patient journey

In an attempt to synthesise the findings from the four countries, we have integrated what is known about the natural history of HCV infection with the successive steps along the care pathway and the involvement of the relevant care providers. This is illustrated further in Figure 5.5.

Figure 5.5 Synthesis of the care pathway mapping



The upper panel in Figure 5.5 describes the standard patient journey of a person newly infected with HCV, and the lower panel of the figure shows the care providers involved at each step of the journey. Primary care physicians, nurses and specialist physicians are often supported by and collaborate with specialist providers who include physicians from other specialties, addiction centres, social care and various NGOs.

Thus the initial diagnosis generally occurs in primary care. Confirmation of diagnosis and decision to initiate (and maintain) treatment occur in specialist care. For advanced (stage of liver fibrosis=F4 or beyond) or complex cases (e.g. co-infection that requires greater expertise), patients are managed in highly specialised services or tertiary care centres, with very advanced cases considered for liver transplantation.

We recognise that the journey depicted in Figure 5.5 presents an ideal type pathway. However, in practice, most cases of HCV infection come to the knowledge of the health service only at advanced disease stages. This is because of the slow progression and asymptomatic character of the infection, so that many people are unaware of having it. The proportion of those unaware of their infection varies among countries, impacted largely by whether countries pursue an active screening policy. The lack of effective screening policies has been identified as one of the greatest barriers to the effective treatment of people with HCV infection. An estimated 75–85% of acute disease cases progress to become chronic because of the protracted course of the infection and because disease complications may only appear decades after contracting the hepatitis C virus (Micallef et al., 2006). As a consequence, the infection is often diagnosed at a late stage when the probability of a successful outcome is reduced.

However, even once people carrying the infection have entered the formal healthcare system, barriers to effective treatment persist. In line with Figure 5.5 these barriers can be identified to impact treatment and care at each tier of health services.

Initial diagnosis, primary care level: There is a notion that lack of awareness among primary care practitioners may impede the effectiveness of early diagnosis and, as a consequence, timely referral to the next care level might be delayed or not take place altogether. It was mentioned in all countries that GPs (and the population) would benefit from awareness campaigns and targeted educational programmes.

Confirmation of diagnosis, specialist care: At the specialist care level, those with suspected HCV infection have their diagnosis confirmed. It is at this level that the decision to treat is made. Treatment involves a regimen of regular assessment and follow-up consultations, and most often PEG INF/RIB combination therapy. It is common that only a small proportion of those found to be eligible for treatment adhere to the regime and return for regular visits. Estimates for England suggest that the proportion of those who are referred is appropriately 70% of cases with the majority of those attending the clinic (70% of those referred) being indicated for treatment; furthermore 70% of these accept treatment; cumulatively just over 30% of those diagnosed actually receive treatment (Ramsay et al., 2011). The reasons for withdrawal from treatment are complex, involving a combination of patient-related factors (e.g. "chaotic" lifestyles of IV drug users who form the majority of patients), treatment-related factors (e.g. side-effects of treatment), clinician-related factors (e.g. failure to provide personalised care) and system-related factors (e.g. lack of coordination of health services with support services for patients).

Treatment of advanced disease stages, highly specialised care: Advanced disease stages or comorbidity pose challenges for both patients and clinicians. We lack evidence to identify specific issues at this level, as those patients constitute only a minority of the cases and interviewees did not highlight barriers to treatment specific to this level.

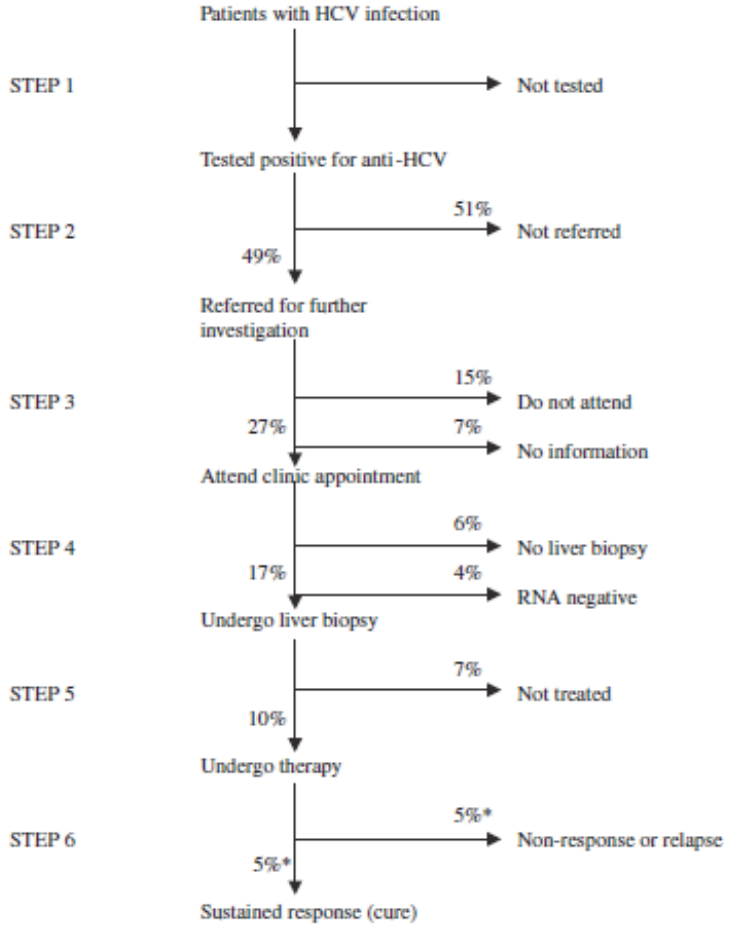
It is worth noting that the new drug developments and more systematic adoption of triple therapy are likely to increase the role of highly specialised care units. This is because a proportion of specialist care providers are unable to deliver new treatments in the first instance because of lack of expertise. However, as treatments become routinised it may be possible that they will be progressively delivered in less specialised centres.

Considering the range of providers involved in providing services along a given patient's journey and the relative complexity of the treatment regimen (involving regular clinic attendance, which may be particularly challenging for some patients with HCV infection), there is a need to strengthen professional collaboration and communication between primary care and specialist care, between different specialist care services, and between health and social care services.

However, there was no clear consensus among interviewees about the quality of the relationships between care providers. Depending on the system context, some felt that currently competition between providers might hinder better coordination as well as the way that systems are organised and financed, while others felt that teamwork was working well. There was also a notion that shortages of selected staff such as specialised nurses might impact on coordination as well as timely clinics and follow-up.

The indicative observations from key informant interviews resonate with the work by Irving et al. (2006). Following up a cohort of newly diagnosed patients from the database of the Nottingham Public Health Laboratory, the authors found that only 10% of the HCV patients were treated, with an even smaller proportion achieving a SVR (5%). This loss to follow-up was explained, largely, by delays in communicating test results, referral issues, and poor coordination between healthcare providers, among other reasons (Figure 5.6).

Figure 5.6 Care pathway for patients with HCV infection[26]



% are calculated from the data in this study except for Step 6, where the figures (*) are estimated on the basis of 50% sustained response rates to therapy [14]

SOURCE: Irving et al., 2006

5.6 Conclusions

Despite variations across countries and issues that are specific to national and regional healthcare systems, the typical journey for HCV patients presents some features that are common to France, Italy, Spain and the UK. The patient journey seems to follow a standardised, while not official, care pathway: the patient enters the healthcare system through primary care or an addiction centre, and is then referred to specialist care for further diagnosis. Thereafter, they are either in outpatient specialist care or hospital specialised units, depending on the healthcare system, the stage of the disease and their

[26] Note: 51% of the infected patients were not referred for reasons including: test results not received or lost; patient refused referral or did not show up to appointment; physician considered the patient not suited for treatment; and patient died.

clinical and behavioural characteristics. Points of departures from this typical journey are mainly due to the limited knowledge of GPs regarding HCV diagnostic tools and decisions, the capacity of the specialist providers to follow up with patients and offer continuity of care, the quality of care coordination and intra-professional collaboration across units, and the motivation and commitment of the patient.

CHAPTER 6 Using discrete choice experiments to quantify physicians' treatment decisions

6.1 Designing the vignettes for the discrete choice experiment

The knowledge generated in the literature review, key informant interviews and patient journey mapping exercise were used to identify essential attributes influencing physicians' decision to treat HCV patients and inform the design of vignettes for the discrete choice experiments. We use the term "vignettes" to describe the combinations of attributes and levels used to describe each of the patient profiles presented within the choice experiments.

The requirements of the discrete choice experiment design and cognitive limits of the respondents placed a restriction on the number of attributes that could viably be included in the experiments, as we were seeking to achieve a balance between the statistical power of the experiment and variety of attributes that would take into account a maximum of parameters. Each attribute was then described by a number of levels, which were also varied in the experiment (from two to six levels per attribute). For example, the stage of liver fibrosis was considered an important factor for treatment decisionmaking, and we defined an attribute with five possible levels: F2, F3, F4 fully compensated, F4 mildly decompensated, and "on the transplant list".

The attributes chosen for inclusion in the choice experiments were based on areas identified in the literature review and key informant interviews components that would be most relevant to decisionmaking, but which may also lead to variation in physicians' actual treatment decisions. For instance, F0 (the initial stage of liver fibrosis) is a factor in physician decisionmaking, and virtually all physicians will not treat someone at this stage, but instead delay treatment. Therefore this was not included as an attribute level in the experiment as it would perfectly explain choices and add little value; instead the levels started with F2, when the decision to treat or to delay treatment is not so obvious and was believed to vary between physicians.

As detailed in Section 2.5.1, each physician was asked to participate in two experiments. In the first choice experiment, which looked at the attributes influencing the decision about commencement of treatment, the following attributes were considered:

- patient characteristics: gender, age, Body Mass Index (BMI)
- patient background: history of substance abuse, stability of living arrangements, social support network, dependants, motivation

- clinical results: genotype, stage of fibrosis, blood results (haemoglobin, platelet count, white cell count)
- comorbidities: psychological disorders, diabetes, HIV, renal disease.

The second choice experiment, which looked at the factors influencing the continuation of treatment (with combination therapy), included:

- all of the patient factors considered in the commencement experiment
- weeks under treatment
- RNA response
- changes in blood results (haemoglobin, platelet count, white cell count)
- patient adherence
- severity of side-effects

The complete list of the levels examined for each of these attributes can be found in Appendix E (Table E.1 and Table E.2). As discussed in Section 2.5.1, a statistical experimental design was developed to specify the combinations of attribute levels to use in defining the vignettes. Some restrictions were placed on this design to prevent infeasible combinations within the levels of fibrosis and anaemia, and levels of fibrosis and platelet count. This introduced a low, but realistic, level of correlation between these attributes within the experimental design.

An example of a vignette for the first experiment is provided in Figure 6.1 below. Each physician was asked to consider nine such vignettes and indicate for the patient in question whether they would decide to commence treatment or not.

Figure 6.1 Example of a vignette: Discrete Choice Experiment 1

This card provides information about a hypothetical patient with a diagnosed case of Hepatitis C.
After reviewing their case given the information below, would you recommend this patient to initiate treatment?

Patient Information	
Gender	Male
Age	30
BMI	32 kg/m^2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	Patient has no social-support network
Dependants	Patient has dependants who need support
Patient's motivation	Patient has reservations about treatment due to cultural/ethic background
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F3
Haemoglobin (anaemia)	8.5–10g/dl
Platelet count	80, 000–100, 000/mm^3
White cells count/neutropenia	< 500/mm^3
Co-morbidities	
Psychological disorders	Ongoing episodes of psychosis, currently under treatment
Other co-morbidities	Type-I diabetes

? **Yes, I would recommend this patient to initiate treatment**

? **No, I would not recommend this patient to initiate treatment**

The second experiment considered the decision to continue or change treatment as time progresses. For this, we took forward up to three of the patient profiles which the physician had indicated he or she would decide to treat in the first experiment. This ensured that the patients then being considered in this decision were patients who the respondent would have been prepared to treat in the first place.

In this second experiment the status of the patient was presented a number of weeks later along with updated clinical data and information on behaviour and adherence. The physician was then asked whether he or she would continue, modify or stop the treatment considering the evolution of the disease, comorbidities, haematological test results, and the general response and attitude to treatment. An example of a vignette in this second experiment is shown in Figure 6.2 below. For each hypothetical patient taken forward from the first experiment the physician was asked to consider a sequence of three different ways that their condition may have developed before then moving on to another of the patients who the respondent had indicated he or she would treat. In total the physician was asked to consider up to nine different vignettes within this second experiment (three hypothetical patients with three different developments of their conditions). It is important to note that the treatment regimen under consideration was pegylated interferon alfa and ribavirin, not triple therapy with protease inhibitors.

These choice experiments were embedded within a wider survey that included a range of background questions and ratings questions to measure the physician's perception of the healthcare system within their own country. The design of these questions was mostly informed by the work on the patient journey and the identification of key challenges to

patients within these systems. They include questions about collaboration between clinicians from different specialties, the quality and timeliness of referral, the role of nurses, and so on. This information was then considered in developing the models of decisionmaking behaviour to see whether they influenced the decisions being made.

The structure of the survey was:

1. Questions on the physician's characteristics:
    - age
    - country
    - speciality
    - clinical setting
    - years since qualifying
    - years of experience with HCV
    - whether has overall responsibility for HCV care
    - number of HCV patients seen per year
2. Questions on their unit's characteristics:
    - whether includes specialist nurses
    - links with health professionals from other specialties
    - links with non-clinical services providers
    - who is consulted in treatment decisions
3. Open-ended discussion of types of treatment used within unit for HCV and barriers to starting treatment
4. Choice experiments
5. Ratings of healthcare system and HCV treatment within own healthcare system.

The exact wording used for the background questions can be found in Appendix E (Table E.3 and Table E.4). These were translated so that the survey was available in English, French, Italian and Spanish.

The surveys were piloted with 13 physicians drawn from across the four target countries to test the process of interviewing, wording of the questions, and viability of the choice experiments prior to rolling out the main survey. From this pilot we concluded that the survey was working broadly as intended and generated useful data for gaining insight into the decisionmaking processes. However, we did identify that there were some combinations of attribute levels in the choice experiments that were clinically unusual. As a result we imposed some additional constraints in the experimental design to avoid situations where F2 or F3 patients were presented with anaemia or very low platelet counts.

Figure 6.2 Example of a vignette: Discrete Choice Experiment 2

You previously recommended this patient to initiate treatment. Their baseline information is shown in the left-hand side of the screen.
The right-hand side of the screen shows their clinical results, compliance with treatment and side-effects following 20 weeks of treatment with pegylated interferon alfa and ribavirin.
After reviewing their case using the information provided in this card, would you recommend this patient to continue treatment?

BASELINE INFORMATION	
Patient Information	
Gender	Male
Age	30
BMI	32 kg/m^2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	Patient has no social-support network
Dependents	Patient has dependents who need support
Patient's motivation	Patient has reservations about treatment due to cultural/ethnic background
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F3
Haemoglobin (anaemia)	8.5–10g/dl l
Platelet count	80,000–100 ,000/mm^3
White cells count/neutropenia	< 500/mm^3
Co-morbidities	
Psychological disorders	Ongoing episodes of psychosis, currently under treatment
Other co-morbidities	Type-I diabetes

Weeks under treatment	20
Response to treatment (HCV-RNA)	Positive RNA (> 2 log drop)
Clinical results	
Haemoglobin (anaemia)	< 8.5g/dl
Platelet count	40 000–60 000/mm^3
White cells count/neutropenia	500–750/mm^3
Side effects	
Patient's compliance	Patient is unreliable in their compliance with treatment
Severity of side-effects	No significant side effects to date

? **I would recommend that the patient continues with their treatment**
? **I would recommend that the current dosage should be increased**
? **I would recommend that the current dosage should be decreased**
? **I would recommend that the patient stops treatment**

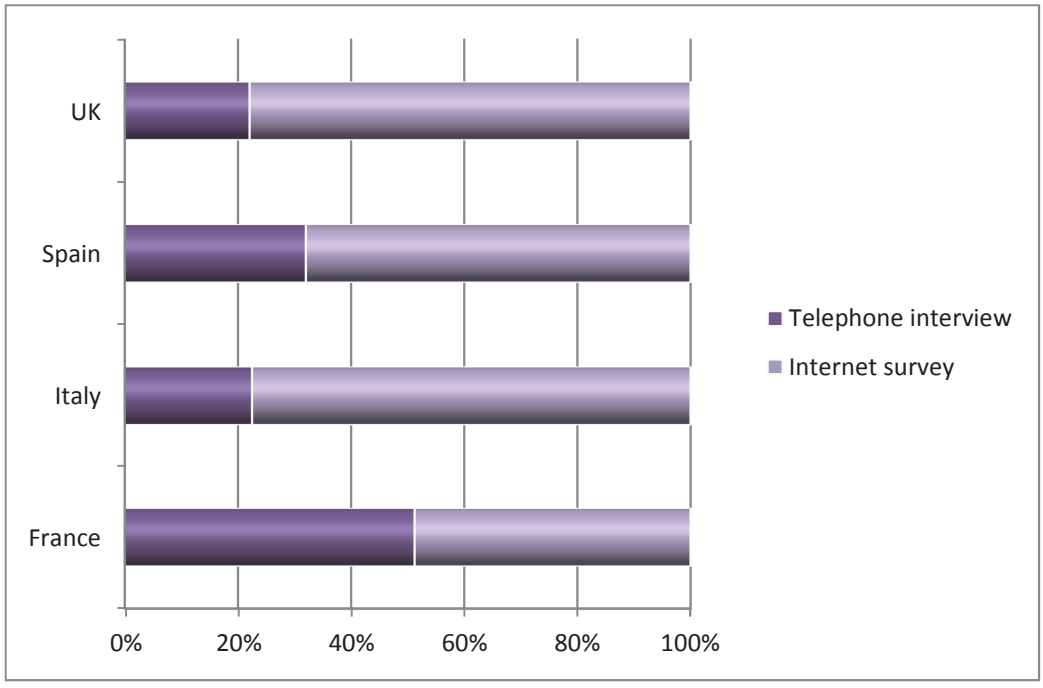
Conduct of the surveys

The survey recruitment process was conducted and managed by Baird's CMC through in-country presence in each location where the survey was conducted. Physicians and specialists nurses were recruited to participate in the study by an initial phone call to make contact with the healthcare professionals and discuss the study. This was then followed up using one of two survey approaches: a personalised link to access an online survey at their convenience, or a further phone call to conduct the survey over the telephone (Figure 6.3). Telephone and online surveys were conducted in the native language of the practitioner, with the telephone interviews undertaken by a native language speaker.

In specifying the sample frame, quotas were set to seek to achieve an equal distribution across countries and a split of one-third senior physicians to two-thirds more junior physicians. A screening question was included at the start of the survey to ensure that the respondent had a role in influencing patient treatment decisions; those who only focused on care once within treatment were deemed out of scope for the study.

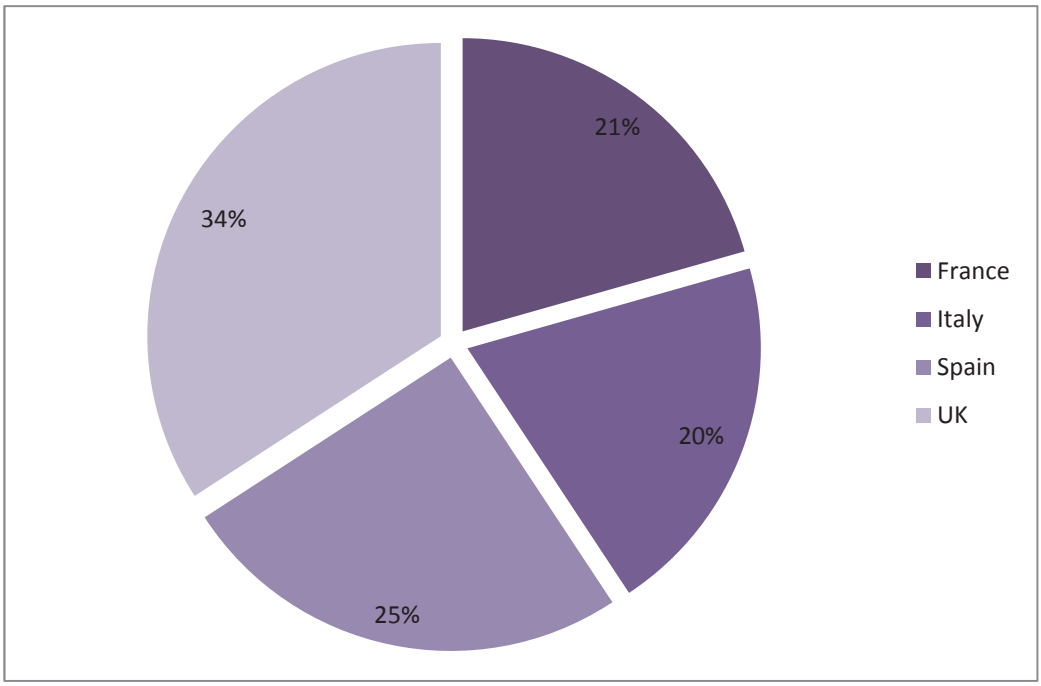
The telephone interviews were predominantly used to target senior physicians; however, the availability of the web survey option allowed greater flexibility to allow individuals to complete the survey at their convenience and over multiple sessions.

Figure 6.3 Mode of survey completion, by country



Across the four countries 210 surveys were undertaken (including the 13 from the pilot phase of the study). The original aim was to collect 200 surveys split equally across the four countries (50 surveys per country), but because of difficulties in recruitment, particularly in France and Italy, healthcare professionals were oversampled in the UK and Spain to compensate and ensure the total number of required surveys was achieved (Figure 6.4).

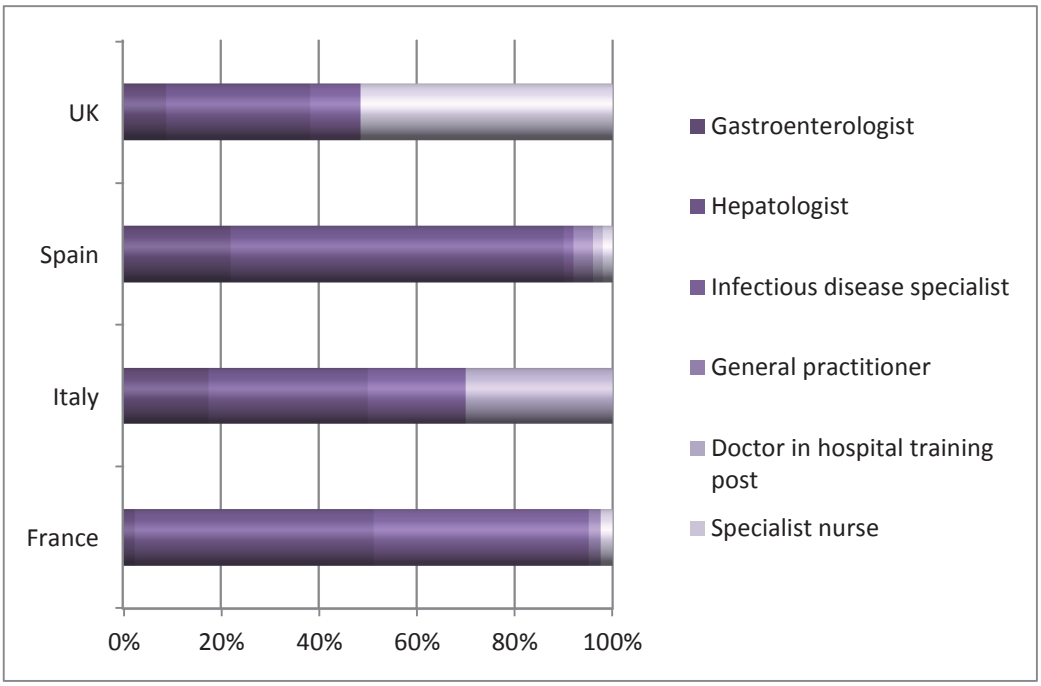
Figure 6.4 Proportion of data from each country involved in the study



6.2 Characteristics of the sample of respondents

In the UK, 52% of the sample was made up of specialist nurses. These are not as common in the other countries surveyed and would not always be involved in making or supporting treatment decisions, and therefore were often not eligible for the survey. As a result this in part reflects a different model of care, where within the UK system some nurses are actively involved in treatment decisions; however, a high proportion of UK nurses within the sample were also influenced by the size of the pool of UK HCV physicians who could be drawn upon.

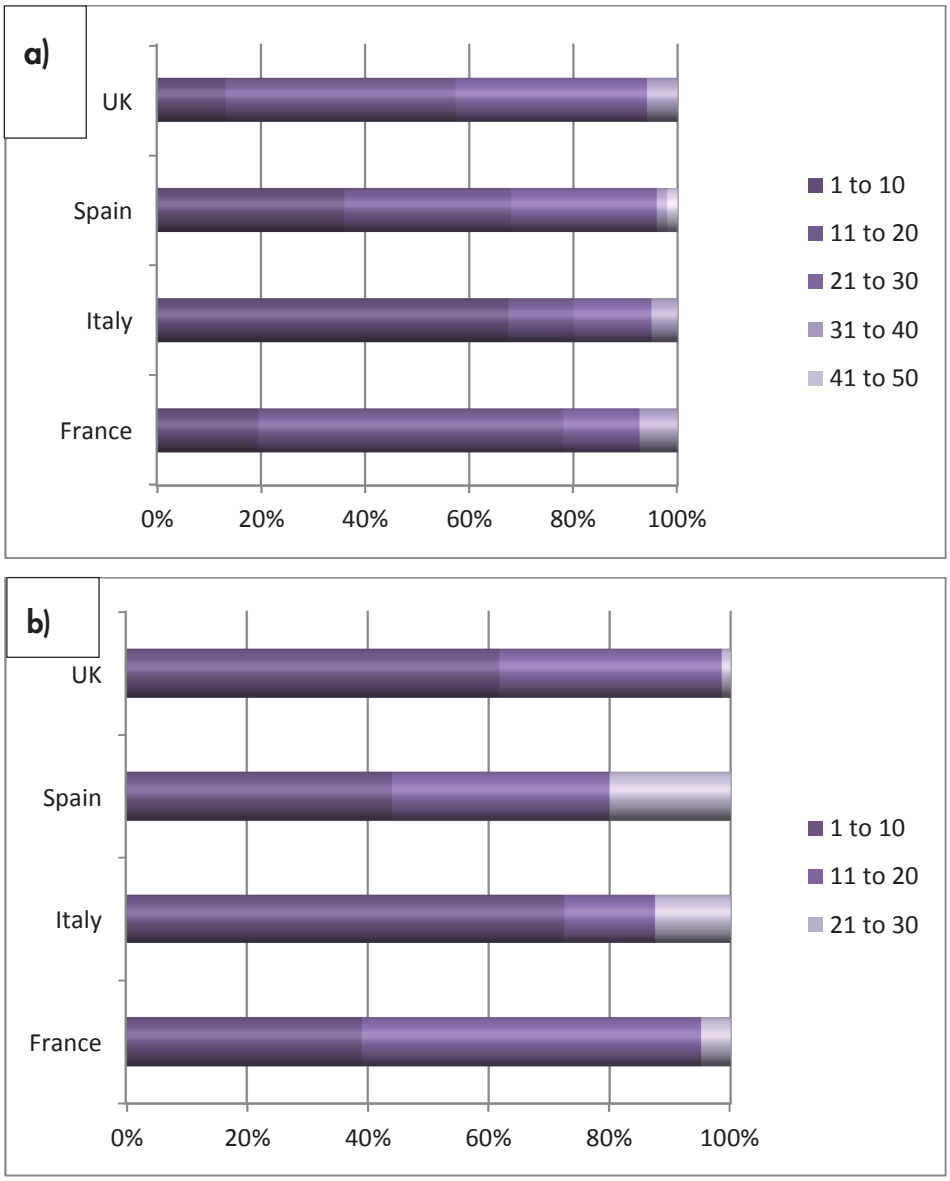
Figure 6.5 Specialisations of respondents, by country



The survey gathered data regarding the level of experience and responsibility the respondents had in their unit. The level of experience varied across respondents and countries, with respondents from the UK and France having proportionally more experience than respondents from Spain and Italy, based on number of years since qualifying. However, the sample of respondents from France and the UK has fewer individuals than Spain or Italy who have specialised in HCV for more than 20 years (Figure 6.6).[27]

[27] As the existence of HCV was postulated in the 1970s and proven in 1989, we would not expect to see physicians stating experience exceeding 21–30 years of specialisation in this area.

Figure 6.6 Level of experience of respondents (a) years of experience since gaining a medical or nursing qualification (b) years of specialised care of patients with HCV, by country



Questions were also asked regarding the level of responsibility that respondents had and their role in making treatment decisions. The higher numbers of individuals solely responsible for decisions in their unit and who make decisions on their own suggest that there is more autonomy in the Spanish and French system (Figure 6.7 and Figure 6.8). This illustrated differences in the sample which were indicative of different practices in different counties. For example, just over 50% of the UK sample is made up of specialised nurses, which accounts for the larger proportion of respondents who stated that overall responsibility for HCV patient care lay with another clinician. In addition, when asked about who else was involved in the treatment of patients with HCV, the results show that there were much higher levels of reported integration of non-clinical services in the UK and France than in Spain and Italy (Figure 6.9).

Figure 6.7 Interviewees' overall responsibility for unit's HCV patient care, by country

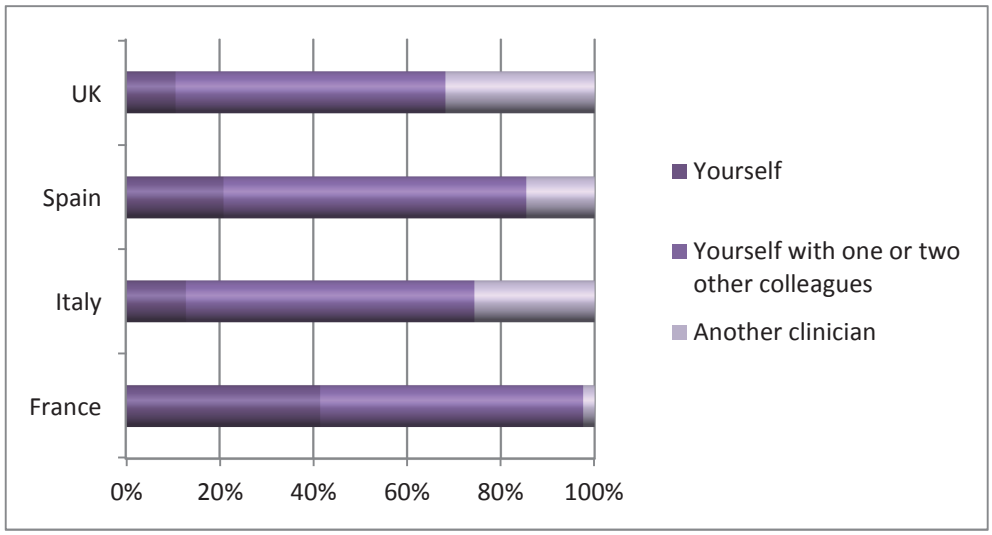


Figure 6.8 Method for decisionmaking process on initiating or changing treatment for patients with HCV, by country

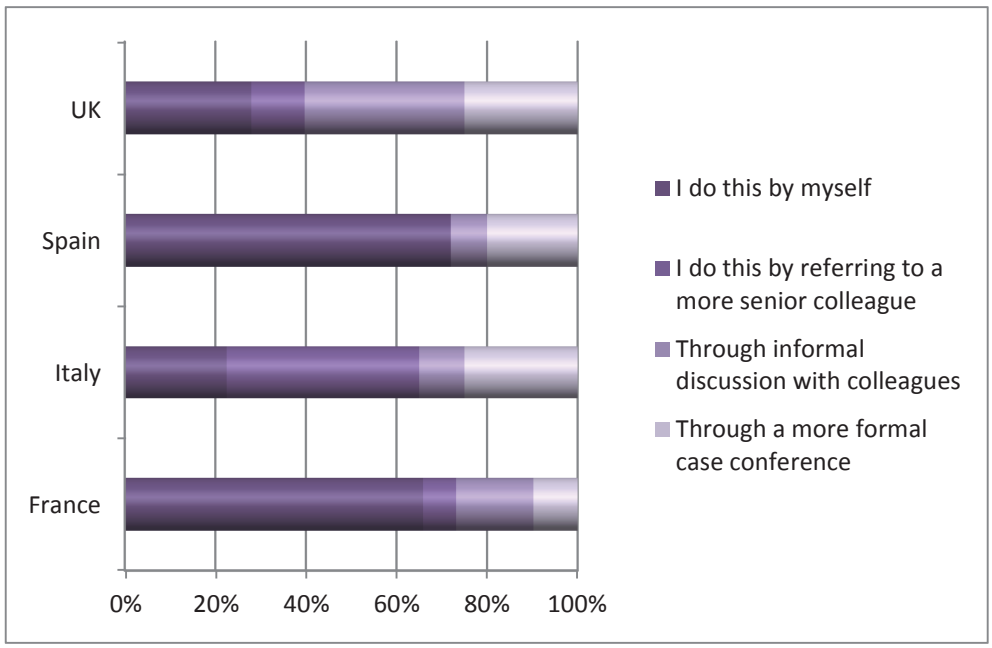
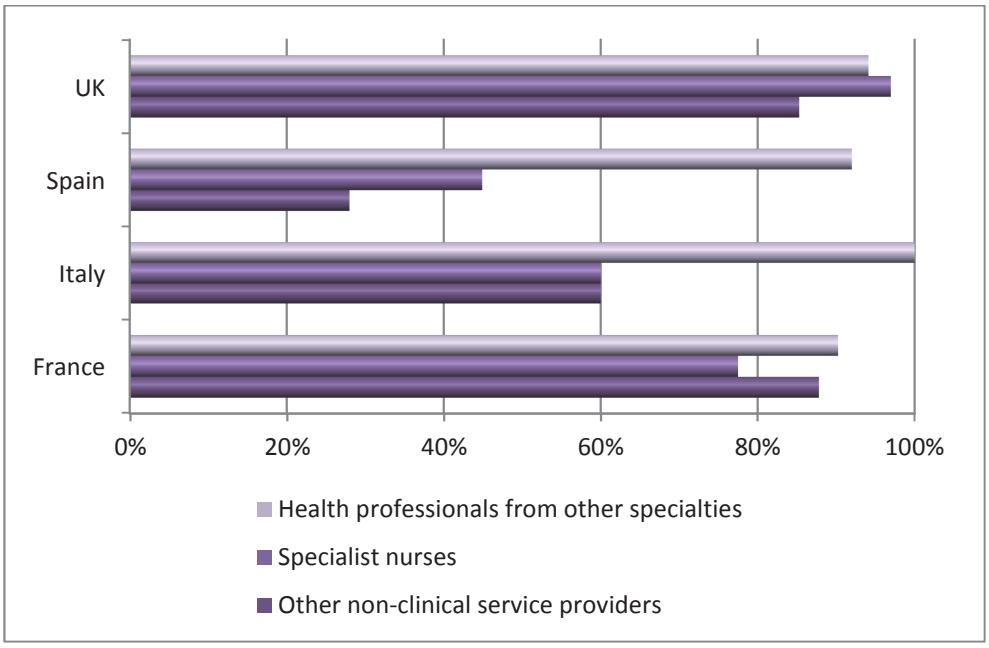
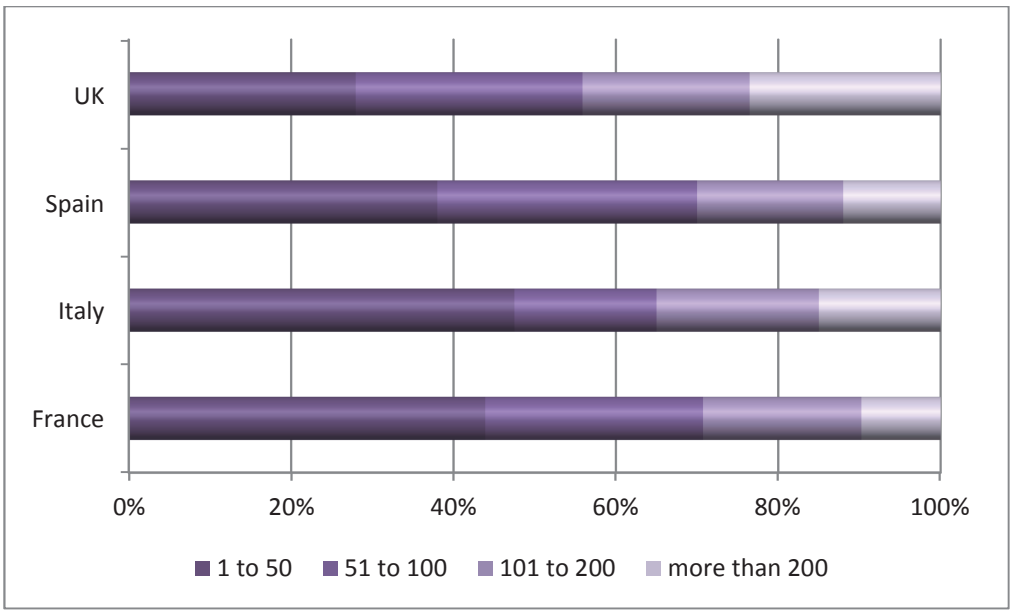


Figure 6.9 Types of individuals identified by HCV specialists as involved in HCV treatment, by country



Reported caseloads were similar throughout the countries surveyed, as indicated by the number of patients seen (Figure 6.10) and illustrated that the sample had captured a diverse range of experience within each country with some physicians seeing up to 50 and others seeing over 200 patients with HCV per year.

Figure 6.10 Number of HCV patients seen per year, by country



6.3 Physicians' perceptions of their health systems and HCV treatment

Physicians were asked to rate aspects of health system within which they worked (Figure 6.11, below). Factors were rated on a scale of 1 to 5:

1 = Very poor, 2 = Poor, 3 = Neutral, 4 = Good, 5 = Very good

In general, across the countries, physicians felt positively about the access to care within their system (Figure 6.11a) but were less positive about their system's ability to identify and test patients at risk (Figure 6.11b). Once identified, the referral pathway is seen as good, although this sentiment is slightly weaker in the Italian system (Figure 6.11c). There was variation in the physicians' experience or expectation of waiting times. French and Spanish physicians were more critical and negative about the waiting times in their systems than physicians in Italy and the UK (Figure 6.11d). There was almost unanimous agreement from specialists that they provide good care (Figure 6.11e), but recognition that each healthcare system struggled to cater for those with chaotic lifestyles and to manage non-attenders, especially in Spain (Figure 6.11f).

There are significant differences in the structure of care and support for patients. The physicians from the UK were predominantly positive regarding the use of support services, reflecting the use of specialist nurses, and their presence in the survey. Those from France were more positive than those from Spain and Italy regarding the use of support services to provide better care to HCV patients (Figure 6.12a). In France, Spain and the UK, over 50% of respondents felt that the level of resource for HCV treatment was good or very good. However, Italian physicians were less satisfied with the level of resources, reporting greater constraints (Figure 6.12b), which reflects the issues reported throughout the key informant interviews (Chapter 4). A generally high level of adherence to guidelines was reported across all countries, though the figure was slightly lower in Italy with only 77% reporting good or very good adherence, compared with 89% across the other three countries surveyed (Figure 6.12c).

Data regarding perceptions of the effectiveness of collaboration between specialisms and between health and social care were also collected. Across all countries, collaboration between specialisms was generally viewed as effective, with an average of 80% of respondents rating collaboration across specialisms as good or very good (Figure 6.12d). Physicians from the UK rated effectiveness of collaboration slightly higher than those from the other countries, with 88% of respondents viewing it as good or very good. However, there were significant difference within and between countries on physicians' perceptions of the effectiveness of collaboration between health and social care sectors (Figure 6.12e). Across all countries, only 40% viewed collaboration across sectors as good or very good and this figure was as low as 12.5% in Spain. Finally, physicians were asked to rate access to care for special population groups, such as the homeless, and drug and alcohol users. Again, their perceptions were mixed but access for these populations is seen as a particular issue in Spain and Italy (Figure 6.12f). This is a different picture from the overall access to care (Figure 6.11a) where an average of 86% of physicians felt positive about their system (rating it good or very good).

Figure 6.11 Physicians' perceptions on aspects of HCV treatment within health-care system a) overall access to care for patients with HCV, b) identification and testing of patients at risk of HCV infection, c) effectiveness of the referral pathway to treatment, d) waiting time from referral to the clinic, e) overall quality of care for patients with HCV once in specialist care, f) ability to manage non-attenders and those with chaotic lifestyles, by country

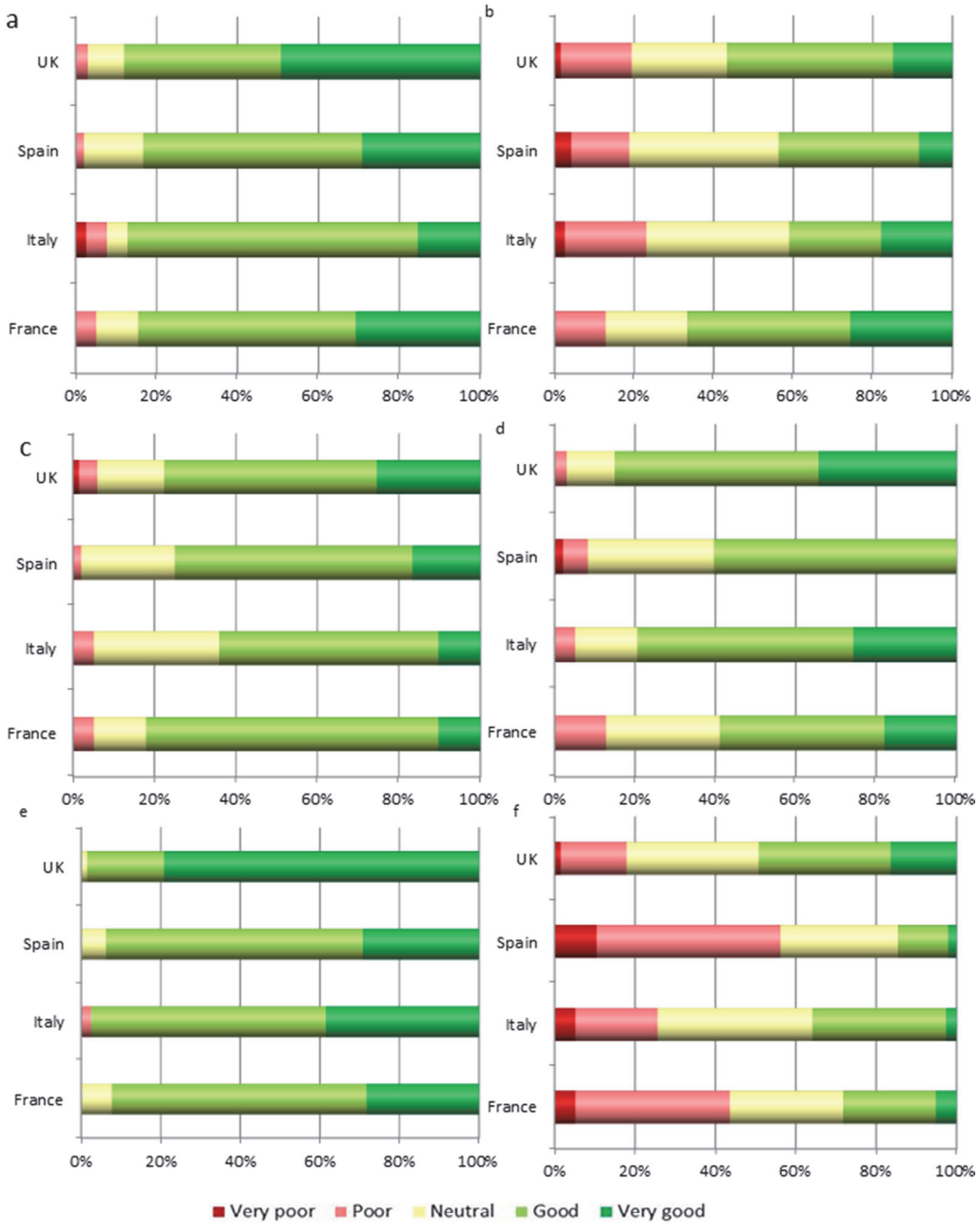
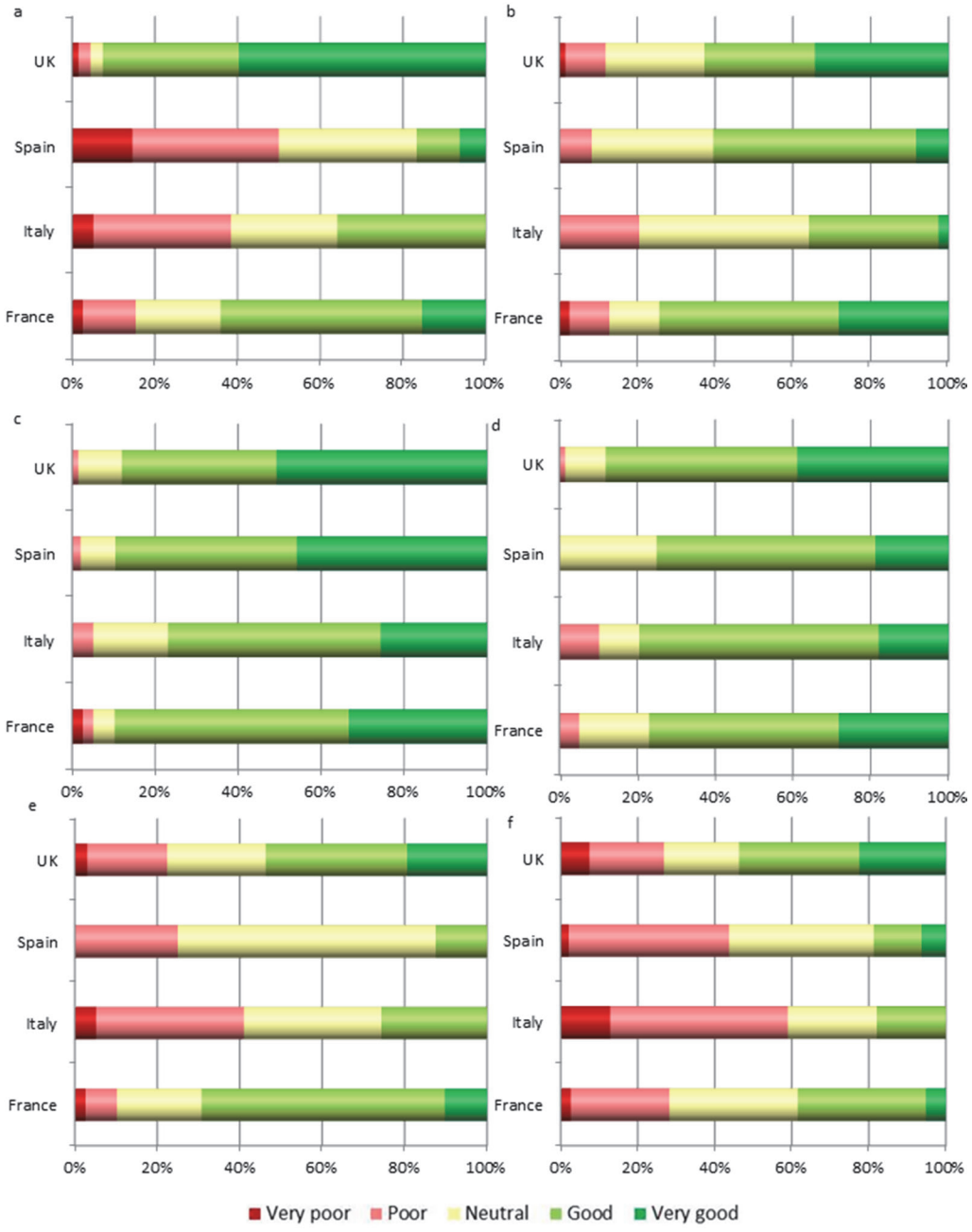


Figure 6.12 Physicians' perceptions on aspects of HCV treatment within health-care system a) support services for patients b) overall level of resources dedicated to HCV, c) level of adherence to national and European clinical practice guidelines, d) effectiveness of collaboration between specialties, e) effectiveness of collaboration between the health and social care sectors, f) level of access to care, and quality of care, for special population groups, by country



6.4 Quantifying the influence of patient characteristics through econometric models of decisionmaking

The data collected through the choice experiments allowed us to estimate a series of discrete choice models to explain the influence that each of the patient and physician characteristics had on the hypothetical decisions made in the experiments. The theory behind these models is explained in more detail in Section 2.5 along with an overview of the steps undertaken in developing the model specifications.

In this section we present the models developed from the choice data along with an interpretation of what these models reveal about what physicians have told us about the decisions that they would make around treatment.

The tables summarise the models with the best specification, as judged through model fit. They show the estimated coefficient value for each model parameter, along with its t-ratio (after bootstrapping to take account of multiple responses per individual).

The summary statistics which are presented for each model are defined in Table 6.1.

Table 6.1 Summary statistics of econometric models of physicians' decisionmaking about HCV treatment

Statistic	Definition
Observations	The number of observations included in the model estimation.
Final log (L)	This indicates the value of the log-likelihood at convergence. The log-likelihood is defined as the sum of the log of the probabilities of the chosen alternatives, and is the function that is maximised in model estimation. The value of log-likelihood for a single model has no obvious meaning. However, comparing the log-likelihood of two models with different specifications allows the statistical significance of new model coefficients to be assessed properly.
DOF	Degrees of freedom, the number of coefficients estimated in this model. Note that if a coefficient is constrained to a fixed value (indicated by (*)) then it is not a DOF.
$Rho^2(0)$	The rho-squared measure compares the log-likelihood (LL(final)) to the log-likelihood of a model with all coefficients restricted to zero (LL(0)): $Rho^2(0) = 1 – LL(final)/LL(0)$ A higher value indicates a better fitting model.

In interpreting the coefficient values the following points should be considered:

- *A positive coefficient* means that the variable level or constant leads to a higher probability of choosing the alternatives to which it is applied.
- *A negative coefficient* means that the variable level or constant leads to a lower probability of choosing the alternative to which it is applied.
- *Some coefficients are multiplied by continuous variables* and therefore reflect the influence of a unit change of the variable, e.g. age of patient, which reflect the relative impact of each year and the influence this has on reducing the probability to treat.
- *Some coefficients are applied to categorical variables*; these therefore reflect the influence of a step change in that variable, relative to a base situation, e.g. the impact of having a history of alcohol or drug misuse compared with the base situation where there is no history of misuse.
- *The constants in each model* reflect preferences for the alternatives to which they are applied. For example, the constant for "Has overall responsibility for HCV patient

care in unit" in the model from the second experiment has a positive value of 0.584 and so implies that these physicians are more likely to cease treatment across the vignettes considered than those who do not have overall responsibility.

- *A positive value for a constant* indicates that the respondent is *more likely* to choose that alternative, and a *negative value* indicates that the respondent is *less likely* to choose that alternative.
- *The constants on the models are additive* and more than one constant can be applied to each decisionmaker.

The value shown in brackets after each coefficient estimate is the t-ratio. This defines the (statistical) significance of the coefficient estimate; regardless of the sign, the larger the t-ratio, the more significant the estimate. A coefficient with a t-ratio greater than +/–1.960 is estimated to be significantly different from zero at the 95% confidence level. A t-ratio of +/–1.645 is significantly different from zero at the 90% confidence interval. In the model estimation procedure we have used the 95% confidence interval coupled with professional judgement to determine which coefficients to retain in the model.

6.4.1 Model of physician decisions around the commencement of treatment

In this section we consider the results from the first choice experiment, which focused on whether the physician would decide to treat a given patient contingent on the profile of that patient. We see from the model results presented in

Table 6.2 that there is a wide range of factors that act to influence the decision whether or not to treat. These results are interpreted in the paragraphs that follow.

Table 6.2 Model results of physicians' decisions on commencement of HCV treatment

	Treat	Don't treat
	Coeff (t-ratio)	Coeff (t-ratio)
Gender		
Male	0.000 (n/a)	
Female	0.000 (n/a)	
Age		
<45 years	0.000 (n/a)	
45–70 years (additional influence per year of age)	−0.032 (−6.0)	
>70 years (additional influence per year of age)	−0.152 (−4.4)	
BMI		
17–32 kg/m^2	0.000 (n/a)	
35 kg/m^2 (compared with BMI of 17–32kg/m^2)	−0.578 (−2.4)	
History of drug or alcohol misuse		
No history of drug and/or alcohol misuse	0.000 (n/a)	
Past history of drug and/or alcohol misuse	−0.285 (−1.9)	
Ongoing drug and/or alcohol misuse; under treatment	−0.437 (−3.0)	
Ongoing drug and/or alcohol misuse; not under treatment	−1.063 (−7.2)	
Living arrangements		
Has stable living arrangements	0.000 (n/a)	
Does not have stable living arrangements	−0.649 (−5.0)	
Family support		
Has close family support	0.000 (n/a)	
Has no close family support but has support from others	0.000 (n/a)	
Has no social-support network	0.000 (n/a)	
Dependants		
Has dependants who need support	0.000 (n/a)	
Has no dependants who need support	0.225 (2.1)	
Patient's motivation		
Is motivated to undertake treatment	0.000 (n/a)	
Is not particularly motivated to undertake treatment	−0.848 (−6.7)	
Has reservations about treatment due to cultural/ethic background	−0.513 (−3.6)	
HCV genotype		
1	0.000 (n/a)	
2	0.505 (4.5)	
3	0.000 (n/a)	
Stage of disease		
F 2	0.000 (n/a)	
F 3	0.508 (3.2)	
F 4 fully compensated	0.616 (3.9)	
F 4 mild decompensation	0.000 (n/a)	
On the transplant list	0.000 (n/a)	
Haemoglobin		
<8.5g/dl	0.000 (n/a)	
≥8.5g/dl	0.510 (3.1)	
Platelet count		
≤70,000/mm^3 (influence per 1000/mm^3)	0.018 (5.0)	
>70,000/mm^3 (additional influence per 1000/mm^3)	−0.018 (−5.0)	
White cell count		
<500/mm^3	0.000 (n/a)	
≥500/mm^3	0.257 (2.2)	
Psychological disorders		
No history of psychological disorders	0.000 (n/a)	
Past history of mild depression and psychological disorders	0.000 (n/a)	
Ongoing mild depression and psychological disorders, currently under treatment	0.000 (n/a)	
Past history of psychosis	−0.542 (−3.9)	
Ongoing episodes of psychosis, currently under treatment	−1.314 (−5.9)	

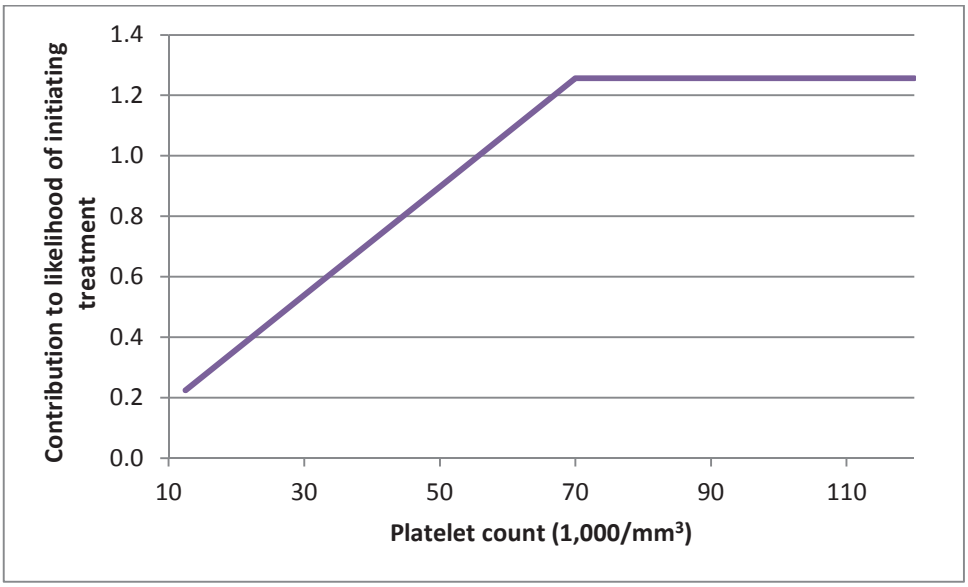
Other comorbidities		
None	0.000 (n/a)	
Type-I diabetes	0.000 (n/a)	
HIV	0.000 (n/a)	
Renal disease	0.000 (n/a)	
Constant on "don't treat"		
France		0.252 (0.7)
Italy		1.665 (4.8)
Spain		1.626 (4.1)
UK		0.731 (2.0)
Model summary statistics		
Observations	1890	
Final log (L)	−986.0	
DOF	22	
Rho²(0)	0.247	

From this model we can observe a number of important points. The first is that there are a number of patient factors which have not been found to have a statistically significant impact on the choices that physicians made in the choice experiment. We see that gender, social support networks and the comorbidities considered were not found to have a significant impact on the decision whether to treat. This does not mean that such effects may not exist, but that we have not been able to identify them within the sample available, which would suggest that any influence they may have would be small.

However, we do see that there is a wide range of other factors that do have a statistically significant influence on the decision to treat. This includes the patient's age, whether or not they are severely obese (BMI of 35kg/m^2), their history of drug or alcohol misuse, whether they have stable living arrangements, whether they have dependants who require support, their level of motivation, and any history of psychosis, along with clinical considerations such as their genotype, the stage of the disease, their haemoglobin, platelet and their white cell counts. These influences all work in the anticipated direction.

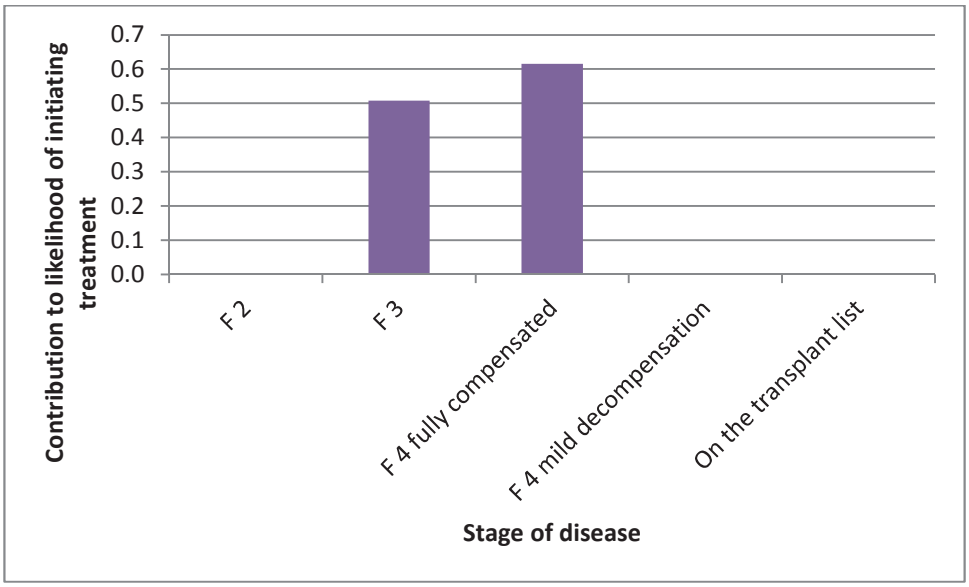
The relationship between platelet count and decision to treat is non-linear. The best model fit to the data uses a piecewise linear specification which allows a positive value to be placed on the increase in platelet count up to a level of 70,000/mm^3, and which then plateaus thereafter showing value placed on further gains in platelet count. It should be noted, however, that the value of 70,000/mm^3 relates to the midpoint of the band 60,000–80,000/mm^3, and that it is possible that the influence of platelet count declines at some other point within that band. This is illustrated below in Figure 6.13. This shows that TCP leads to reductions in the likelihood of treatment, and that interventions that can increase platelet counts up to 70,000/mm^3 will act to increase the likelihood that any patient will be considered for initiation of treatment.

Figure 6.13 The relationship between platelet count and weight placed on this when considering whether to treat



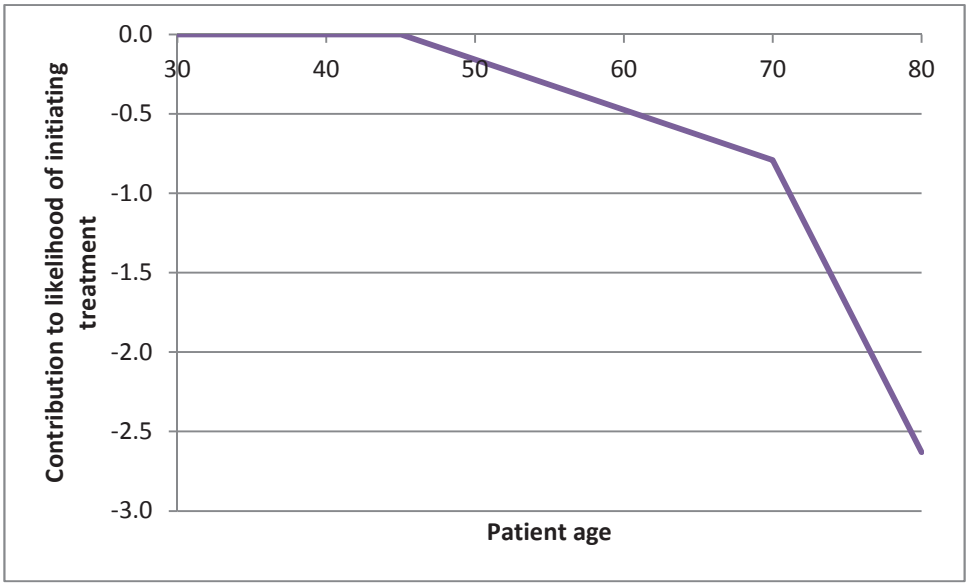
We also observe from the physician decisions that the stage of disease plays a significant role in deciding whether to treat, as illustrated in Figure 6.14. The likelihood of treatment increases as the patient progresses to F3, and then increases further as they reach F4 fully compensated; however, it then declines significantly once the patient experiences decompensation. In the later stages of the disease the impact of the stage on likelihood of treatment returns to the same level as at the very early stages. The model also suggests that across the four countries under consideration the probability of treating those with genotype 2 is significantly greater than those with genotype 1 or 3. It is interesting to note that we did not observe statistical differences between the likelihood of accepting those with genotypes 1 or 3 for treatment.

Figure 6.14 The relationship between stage of disease and weight placed on this when considering whether to treat



We also observe a non-linear relationship between the patient's age and the influence it has on deciding whether to treat. As can be seen from Figure 6.15, physicians were generally insensitive to age when the patient was younger than 45; as age increased beyond the age of 45 it became a factor predicting a reduced probability of treating; and more weight is then placed on this when the patient passes the age of 70.

Figure 6.15 The relationship between patient's age and weight placed on this when considering whether to treat

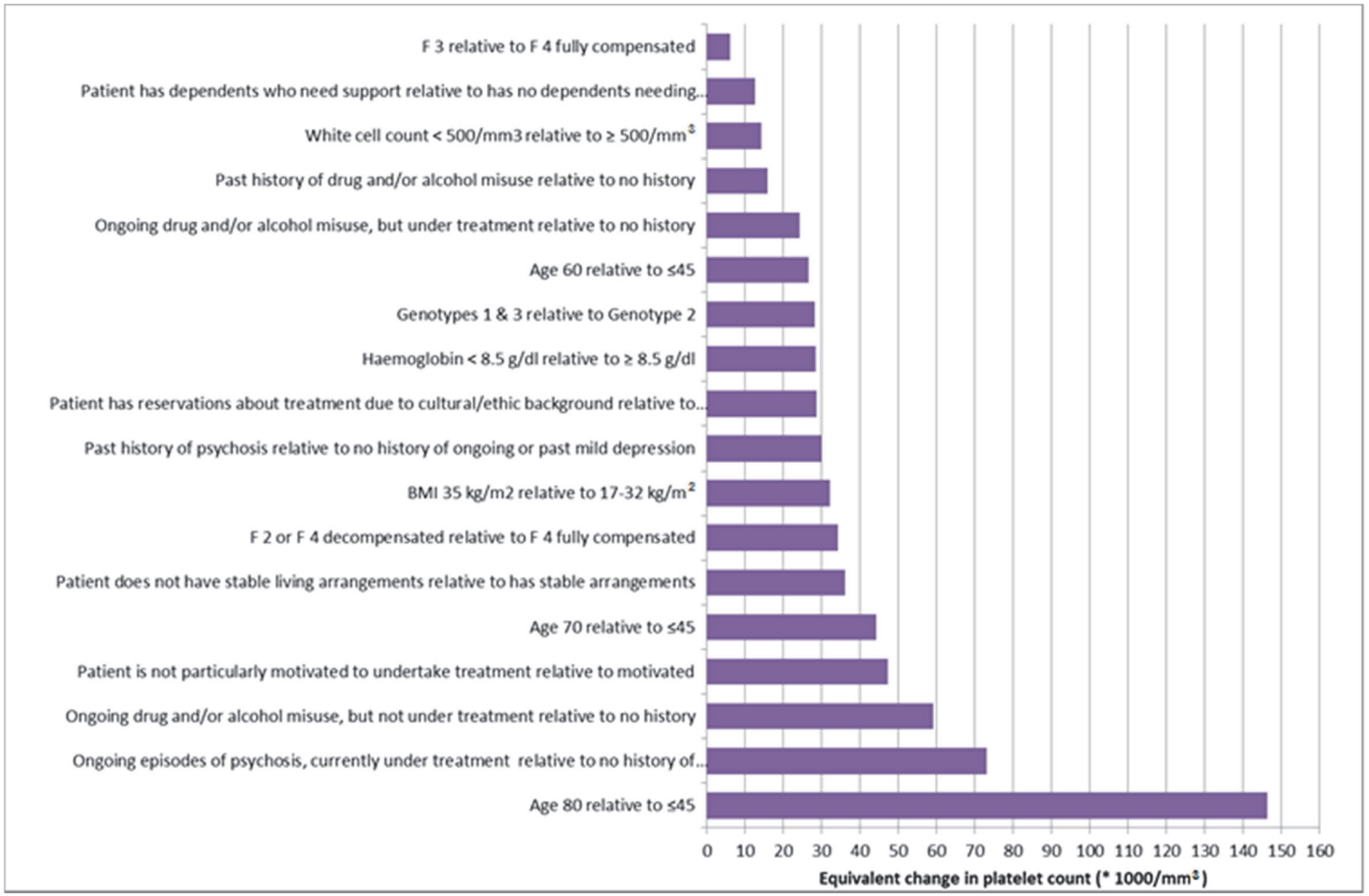


We can also observe that the decision whether to treat varies significantly between countries, independent of the characteristics of the patient being presented for treatment. The model shows that the physicians in France were most willing to treat the patients

presented in the choice task, followed by the physicians in the UK. There was little difference in the willingness to treat between the physicians in Italy and Spain.

Further insight can be gained by considering the weight placed on changes in each of the factors relative to a common "currency", which for the purposes of this example we take as the platelet count (as valued in terms of change in each 1,000 platelets per mm^3 for counts ≤70,000). Figure 6.16 shows the relative value of each of the other factors. For example, from this figure we can observe that if the physician was faced with two patients who were identical in all other ways, apart from one (patient A) having a past history of drug or alcohol misuse, then patient A would need a platelet count that was in excess of 14,000/mm^3 higher than patient B to be considered for treatment over patient B. Similarly, the model from physicians' choices shows that a patient having an ongoing drug or alcohol misuse problem would require a platelet count in excess of 59,000/mm^3 higher than a patient without any history of misuse to be considered for treatment over them (all else being equal).

Figure 6.16 The value of changes in each attribute relative to a change in platelet count



6.4.2 Model of physician decisions around the continuation of treatment

We can consider the results from the second choice experiment, which focused on whether the physician would decide to continue treating a given patient, in much the same way. We see from the model estimated on this data, presented in Table 6.3, that there is a wide range of factors that act to influence the decision whether or not to continue treatment, decrease dosage, or cease treatment altogether.

Table 6.3 Model of physicians' decisions on continuation of HCV treatment

			Continue treatment Coeff (t-ratio)	Decrease dosage Coeff (t-ratio)	Cease treatment Coeff (t-ratio)
Weeks under treatment					
	Per week of treatment				0.261 (7.9)
	Additional influence per week if ≥12 weeks				−0.221 (−3.9)
Response to treatment					
	Positive RNA (>2 log drop)				0.000 (n/a)
	Positive RNA (<2 log drop) [France, Italy, UK]				1.463 (7.0)
	Positive RNA (<2 log drop) [Spain]				0.000 (n/a)
	Negative RNA [France, Italy, UK]				−2.963 (−6.9)
	Negative RNA [Spain]				−1.215 (−2.0)
Haemoglobin					
	Was	**Now**			
	<8.5 g/dl	same or higher	0.000 (n/a)	0.000 (n/a)	0.000 (n/a)
	8.5–10 g/dl	same or higher	0.812 (4.1)	0.000 (n/a)	0.000 (n/a)
	8.5–10 g/dl	<8.5 g/dl		1.509 (7.6)	0.867 (4.4)
	>10 g/dl	same or higher	0.516 (2.6)	0.000 (n/a)	0.000 (n/a)
	>10 g/dl	8.5–10 g/dl		0.539 (2.2)	0.000 (n/a)
Platelet count					
	Was (for each 1,000/mm^3)		0.005 (1.9)		
	Was	**Now**			
	<25,000/mm^3	same or higher		0.000 (n/a)	0.000 (n/a)
	25,000–40,000/mm^3	same or higher		0.000 (n/a)	0.000 (n/a)
	25,000–40,000/mm^3	<25,000/mm^3		1.665 (5.0)	0.670 (1.9)
	40,000–60,000/mm^3	same or higher		0.000 (n/a)	0.000 (n/a)
	40,000–60,000/mm^3	25,000–40,000/mm^3		0.990 (2.2)	0.000 (n/a)
	40,000–60,000/mm^3	<25,000/mm^3		0.616 (1.1)	1.834 (2.3)
	60,000–80,000/mm^3	same or higher		0.000 (n/a)	0.000 (n/a)

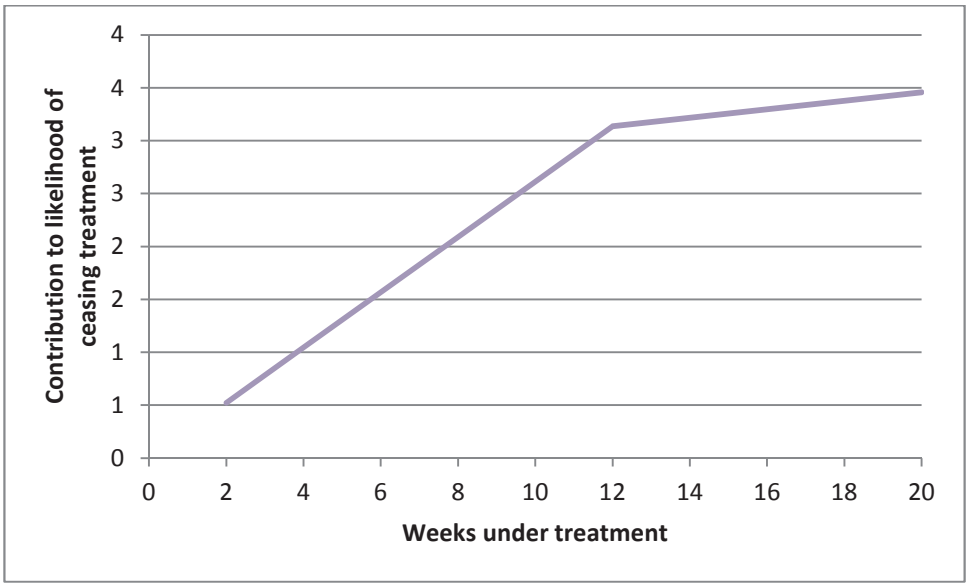
	60,000–80,000/mm^3	40,000–60,000/mm^3		0.348 (1.3)	0.000 (n/a)
	60,000–80,000/mm^3	25,000–40,000/mm^3		0.843 (2.4)	0.489 (1.6)
	80,000–100,000/mm^3	same or higher		0.000 (n/a)	0.000 (n/a)
	80,000–100,000/mm^3	60,000–80,000/mm^3		0.000 (n/a)	0.000 (n/a)
	80,000–100,000/mm^3	40,000–60,000/mm^3		0.632 (2.5)	0.000 (n/a)
	>100,000/mm^3	same		0.000 (n/a)	0.000 (n/a)
	>100,000/mm^3	80,000–100,000/mm^3		0.000 (n/a)	0.000 (n/a)
	>100,000/mm^3	60,000–80,000/mm^3		0.405 (1.8)	0.000 (n/a)
White cell count					
	Was	**Now**			
	<500/mm^3	same or higher	0.000 (n/a)	0.000 (n/a)	0.000 (n/a)
	500–750/mm^3	same or higher	0.000 (n/a)	0.000 (n/a)	0.000 (n/a)
	500–750/mm^3	<500/mm^3		0.538 (2.0)	0.769 (3.0)
	>750/mm^3	same or higher	0.000 (n/a)	0.000 (n/a)	0.000 (n/a)
	>750/mm^3	500–750/mm^3		0.450 (2.3)	0.576 (2.1)
Patient's adherence					
	Fully compliant with treatment			0.000 (n/a)	0.000 (n/a)
	Virtually fully compliant with treatment			0.000 (n/a)	0.000 (n/a)
	Unreliable in adherence to treatment			0.000 (n/a)	0.796 (4.0)
Severity of side-effects					
	No significant side-effects to date			0.000 (n/a)	0.000 (n/a)
	Minor side-effects			0.000 (n/a)	0.000 (n/a)
	Strong but manageable side-effects			0.000 (n/a)	0.000 (n/a)
Constant					
	France			−1.655 (−4.1)	−3.337 (−7.4)
	Italy			−1.009 (−2.9)	−2.892 (−6.0)
	Spain			−0.491 (−1.3)	−3.449 (−6.7)
	UK			−0.625 (−2.0)	−3.430 (−7.8)
Other constants – physician characteristics and opinions					
	Has overall responsibility for HCV patient care in unit				0.584 (1.9)
	Makes decisions about changing treatment through informal discussions with colleagues			−0.820 (−3.4)	
	Rates healthcare system as very good for identification and testing of patients at risk of HCV		0.565 (2.1)		

	infection	
	Rates healthcare system as very good for ability to manage non-attenders and those with chaotic lifestyles	0.530 (2.0)
Model summary statistics		
	Observations	1618
	Final log (L)	−1183.7
	DOF	38
	Rho²(0)	0.334

It is noteworthy that while this second experiment included all of the patient-related factors considered in the first experiment, very few of them were found to play a significant role in the decision as to whether to continue treatment. Generally, if a patient had previously been accepted for treatment by a physician the data suggest that he or she did not then subsequently discriminate in the decision about whether to continue treatment on the basis of the characteristics of the specific patient. The only factors that physicians actually took into account from the baseline decision whether to treat were those associated with their blood tests, i.e. the haemoglobin, platelet and white cell counts. No weight was placed on the socio-demographic or background characteristics of the patients. As a result, these do not appear as significant determinants of the treatment decisions in the model shown in Table 6.3.

As would be expected, we can observe from the model that a patient is less likely to be kept in treatment as time elapses, and if they do not have an appropriate RNA response. The relationship with elapsed time under treatment is also non-linear as can be seen in Figure 6.17. It is also interesting to observe that while the baseline blood characteristics play a significant role, an improvement in any of these since treatment initiation was not observed to increase the probability of continuing treatment. However, a deterioration in either haemoglobin, platelet or white cell counts from baseline are seen as a significant determinant in both the decisions to either decrease dosage or to cease treatment.

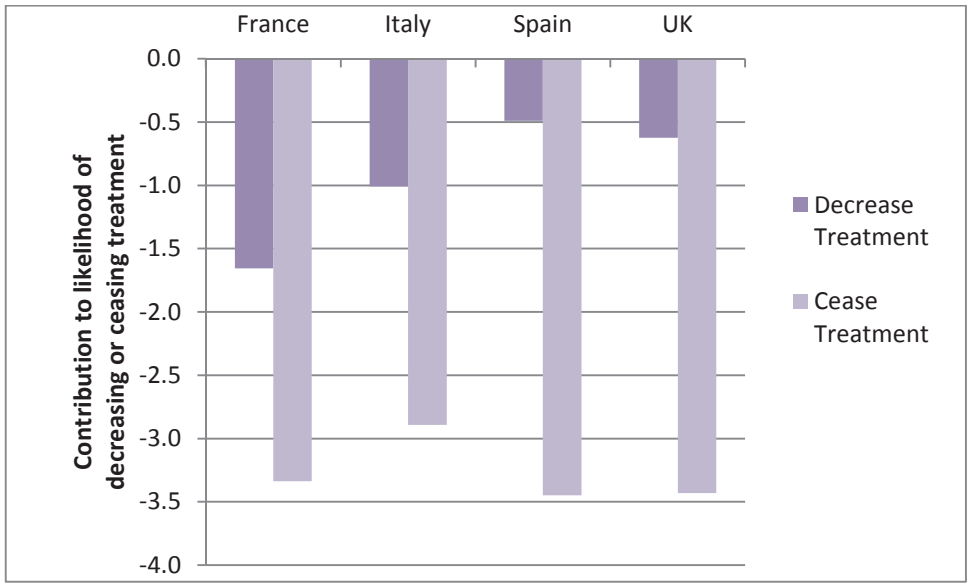
Figure 6.17 The relationship between weeks under treatment and weight placed on this when considering whether to cease treatment



Alongside the consideration of the patient's physiological response, it is clear that physicians also place a high weight on whether the patient is reliable in their adherence to treatment. Those patients who were stated to be unreliable in their adherence are observed within the data to be more likely to have their treatment ceased. However, it is interesting to note that physicians did not make decisions to decrease dosage or cease treatment on the basis of treatment side-effects; it therefore seems likely that given the high awareness of the side-effects that result from this treatment, the physicians took the patient's adherence as an indicator as to the extent to which the side-effects could be tolerated.

It can also be seen that there are differences in propensity to both cease treatment and decrease dosage by country. Figure 6.18 shows the values of the constants on each of the utility functions, and from this it can be observed that the likelihood of decreasing treatment is smallest in France and largest in Spain. In contrast, the likelihood of ceasing treatment is smallest in Spain (closely followed by the UK) and largest in Italy.

Figure 6.18 Influence of country of physician on consideration of whether to decrease or cease treatment, by country



There are also some physician-related characteristics that appear to affect the propensity to continue, decrease or cease treatment, independent of the progress made by the patient. Those physicians who stated that they have overall responsibility for HCV patient care in their unit were more likely to say they would cease treatment than those who did not have overall responsibility within their unit. Those who stated that they make decisions by consulting colleagues were less likely to indicate in the choice experiments that they would decrease dosage. We also see that the way in which physicians perceived the healthcare system within which they were working also had some effects. Those who rated their healthcare system as very good at identifying patients at risk of HCV were more likely to continue treating patients, as were those who felt that their healthcare system was very good at managing non-attenders and those with chaotic lifestyles.

It is less easy to look at the relative weight placed on the various attributes for this experiment as there is no straightforward "currency" against which to compare. Platelet counts still play an important role, but their influence is less straightforward as the count at treatment initiation and then the change in count during the course of treatment both play a role. It would therefore be difficult, and potentially misleading, to produce a similar figure to Figure 6.16 for the model findings from this experiment. As a result, we have set up the models within a forecasting system to better allow the influence of each attribute to be observed; this is reported in the next section.

6.5 Implementation of the models into a forecasting system

The output from each model is a set of coefficients that indicate the influence that each factor has on the likelihood of treating a patient and continuing treatment. However, the magnitude of the influence of these, and how they work in combination in influencing treatment decisions, is not immediately obvious from an examination of the coefficients alone.

These coefficients become more meaningful when the model is set up in an implementation system that allows the variation of a range of factors simultaneously to see whether there are specific profiles of patients who are less likely to be treated. We have therefore programmed the models within an Excel interface to allow an exploration of the differences in probability of treatment across the range of patient profiles covered by the experiments that have been undertaken.

Separate models have been coded for each of the decisions: whether to initiate treatment, and whether to continue treatment. Within the Excel interface it is possible for the user to select different patient characteristics from drop-down menus and select a profile of interest. The spread sheet then uses the utility functions and coefficients from the estimated models to calculate the probabilities of each possible outcome, and presents these separately for each of the four countries within the scope of the study. An example of this is shown in Figure 6.19.

Figure 6.19 Example forecast for probability of HCV treatment being initiated

Model outputs **Select patient profile from drop down lists below …**

Patient Information	
Gender	*No impact on probabilities*
Age	60
BMI	17–32 kg/m^2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	*No impact on probabilities*
Dependants	Patient has no dependants who need support
Patient's motivation	Patient is motivated to undertake treatment
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F4 fully compensated
Haemoglobin (anaemia)	8.5–10g/dl
Platelet count	> 60,000/mm^3
White cells count/neutropenia	500 -750/mm^3
Co-morbidities	
Psychological disorders	No history of psychological disorders or current or past history of mild depression
Other co-morbidities	*No impact on probabilities*

Country in which seeking treatment	France	Italy	Spain	UK
Probability of receiving treatment	91%	72%	73%	87%
Probability of not receiving treatment	**9%**	**28%**	**27%**	**13%**

This system can then be used to examine how the probability of treatment changes for different patient profiles. For example, for the patient shown in Figure 6.19, we can explore the difference in probability of being accepted for treatment if they were instead experiencing severe TCP.

Figure 6.20 Example forecast for patient with lower platelet count for probability of HCV treatment being initiated

Model outputs **Select patient profile from drop down lists below …**

Patient Information	
Gender	*No impact on probabilities*
Age	60
BMI	17–32 kg/m^2
History of drug and/or alcohol abuse	Past history of drug and/or alcohol misuse
Living arrangements	Patient has stable living arrangements
Social support network	*No impact on probabilities*
Dependants	Patient has no dependants who need support
Patient's motivation	Patient is motivated to undertake treatment
Clinical results	
HCV genotype	2
Stage of liver fibrosis	F4 fully compensated
Haemoglobin (anaemia)	8.5–10g/dl
Platelet count	< 25,000/mm^3
White cells count/neutropenia	500–750/mm^3
Co-morbidities	
Psychological disorders	No history of psychological disorders, or current or past history of mild depression
Other co-morbidities	*No impact on probabilities*

Country in which seeking treatment	France	Italy	Spain	UK
Probability of receiving treatment	79%	48%	49%	70%
Probability of not receiving treatment	**21%**	**52%**	**51%**	**30%**

In fact, a range of scenarios can be run to explore how the probabilities of receiving and not receiving treatment change as the platelet count varies.

Table 6.4 The influence of variation in platelet count on probability of HCV treatment for patients considered in Figure 6.19, by country

Platelet count (/mm^3)	France	Italy	Spain	UK
>60,000	91%	72%	73%	87%
40,000–60,000	88%	64%	65%	82%
25,000–40,000	84%	57%	58%	77%
<25,000	79%	48%	49%	70%

Of course, the probabilities of being treated will vary according to the specific patient profile under consideration, and the figures shown in Table 6.4 should only be considered as one possible illustration. However, they do show the influence that platelet count can have on the probability of treatment for an otherwise attractive patient, and how this influence differs between countries.

A similar forecasting system has been set up for the model from the second experiment; an example of this is shown in Figure 6.21.

Figure 6.21 Example forecast for probability of HCV treatment being continued

Model outputs | **Select patient profile from drop down lists below …**

Weeks under treatment	8
Response to treatment (HCV-RNA)	Positive RNA (> 2 log drop)
Clinical results (change from baseline to week x)	
Haemoglobin (anaemia)	Constant at 8.5–10g/dl or increased
Platelet count	Constant at 40,000– 60,000/mm^3 or increased
White cells count/neutropenia	Constant at 500 –750/mm^3 or increased
Patient's compliance	Patient is fully (or virtually fully) compliant with treatment
Severity of side-effects	*No impact on probabilities*
Physician characteristics and opinions	
Has overall responsibility for HCV patient care in unit	Yes
Makes decisions about changing treatment through informal discussions with colleagues	No
Rating of healthcare system for identification and testing of patients at risk of HCV infection	< Very Good
Rating of healthcare system for ability to manage non-attenders and those with chaotic lifestyles	< Very Good

Country in which seeking treatment	France	Italy	Spain	UK
Probability of continuing current treatment	80%	71%	73%	74%
Probability of reducing dosage	5%	9%	15%	14%
Probability of stopping treatment	**14%**	**20%**	**12%**	**12%**

Again, this can be used to explore the influence that each factor has on the probability of remaining in treatment, and to illustrate treatment differences that might be achieved if policies or therapeutic improvements could be used to reduce the chance of an undesirable change in the patient during treatment. We show the influence of two such changes below. In Figure 6.22 we show the impact of the patient experiencing severe TCP during treatment and the probability of the treatment being ceased for each country.

Figure 6.22 Example forecast for a patient experiencing a drop in platelet count during HCV treatment

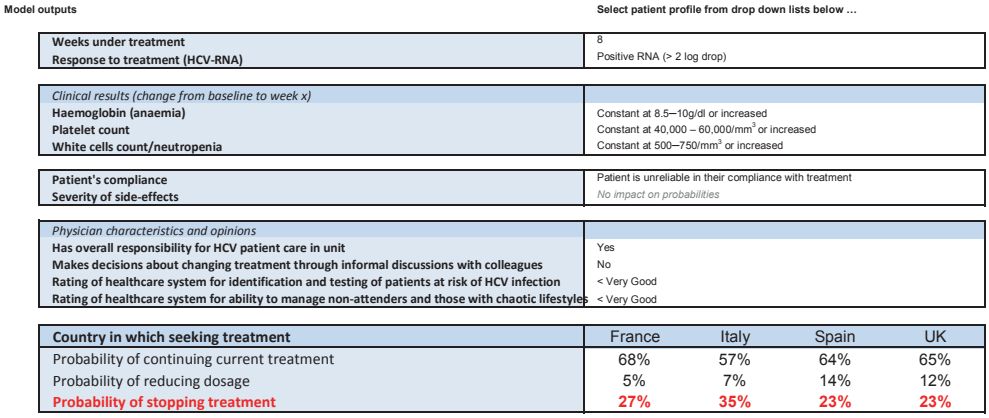
Model outputs | **Select patient profile from drop down lists below …**

Weeks under treatment	8
Response to treatment (HCV-RNA)	Positive RNA (> 2 log drop)
Clinical results (change from baseline to week x)	
Haemoglobin (anaemia)	Constant at 8.5–10g/dl or increased
Platelet count	Decreased 40,000 – 60 000/mm^3? < 25, 000/mm^3
White cells count/neutropenia	Constant at 500 -750/mm3 or increased
Patient's compliance	Patient is fully (or virtually fully) compliant with treatment
Severity of side-effects	*No impact on probabilities*
Physician characteristics and opinions	
Has overall responsibility for HCV patient care in unit	Yes
Makes decisions about changing treatment through informal discussions with colleagues	No
Rating of healthcare system for identification and testing of patients at risk of HCV infection	< Very Good
Rating of healthcare system for ability to manage non-attenders and those with chaotic lifestyles	< Very Good

Country in which seeking treatment	France	Italy	Spain	UK
Probability of continuing current treatment	45%	34%	42%	42%
Probability of reducing dosage	5%	8%	16%	15%
Probability of stopping treatment	**50%**	**59%**	**42%**	**43%**

Similarly, we can see the impact that would be expected if, instead of experiencing TCP, the patient were to retain the same platelet count but became unreliable in their adherence to treatment (Figure 6.23).

Figure 6.23 Example forecast for a patient becoming unreliable in their adherence during HCV treatment



Model outputs	Select patient profile from drop down lists below …
Weeks under treatment	8
Response to treatment (HCV-RNA)	Positive RNA (> 2 log drop)
Clinical results (change from baseline to week x)	
Haemoglobin (anaemia)	Constant at 8.5–10g/dl or increased
Platelet count	Constant at 40,000 – 60,000/mm^3 or increased
White cells count/neutropenia	Constant at 500–750/mm^3 or increased
Patient's compliance	Patient is unreliable in their compliance with treatment
Severity of side-effects	*No impact on probabilities*
Physician characteristics and opinions	
Has overall responsibility for HCV patient care in unit	Yes
Makes decisions about changing treatment through informal discussions with colleagues	No
Rating of healthcare system for identification and testing of patients at risk of HCV infection	< Very Good
Rating of healthcare system for ability to manage non-attenders and those with chaotic lifestyles	< Very Good

Country in which seeking treatment	France	Italy	Spain	UK
Probability of continuing current treatment	68%	57%	64%	65%
Probability of reducing dosage	5%	7%	14%	12%
Probability of stopping treatment	**27%**	**35%**	**23%**	**23%**

These two model systems can be used to run a wide range of different scenarios to explore a wide range of different profiles. The first can be used to understand the probability that patients with different backgrounds and different physiological profiles may be treated within each country. The second gives insight into how the probability of remaining in treatment then varies by country according to the response of the patient during treatment.

This illustrates the power of the modelling exercise in not only showing which factors are important in influencing treatment decisions, but also in quantifying the level of influence that each are likely to have on the basis of the responses we have obtained from the structured choice experiments undertaken with a sizeable sample of physicians across the four countries of interest.

The implementation of the models undertaken above reveals the probability that different profiles of patients will be treated, and then will continue to receive treatment. The application of the models could be further extended to population estimates if combined with good quality epidemiological data that could define the profile of patients being identified with HCV in a country, or a regional health system within any of the studied countries. Extending the application of the models in this way would allow a country-level quantification of the impact of different interventions, be that by improving the attractiveness of patients presenting for treatment through supporting services that may assist in addressing substance dependency or raising patient motivation before treatment, through to pharmacological interventions that may boost haemoglobin, platelet or white cell counts. The practicality of this will be influenced by the availability of epidemiological data for HCV patients in the countries of interest, which provide sufficient information to profile the patient populations across the characteristics considered within this study.

6.6 Conclusions

This study has successfully used discrete choice experiments to explore the influence that a range of patient characteristics have on physician decisionmaking. This provides valuable empirical data from which we have been able to estimate econometric models to explain the weight placed on a range of factors and the trade-offs being made when considering

whether to treat different profiles or patients, and then subsequently whether to continue as the treatment progresses.

6.6.1 Models of the decision to commence treatment

We observe from our models that there is a wide range of other factors that have a statistically significant influence on the decision to treat. They include the patient's age, whether or not they are severely obese (BMI of 35kg/m^2), their history of drug or alcohol misuse, whether they have stable living arrangements, whether they have dependants who require support, their level of motivation, and any history of psychosis, along with clinical considerations such as their genotype, the stage of the disease, and their haemoglobin, platelet and white cell counts. These influences all work in the anticipated direction.

The relationship between platelet count and decision to treat is non-linear. The evidence from our study suggests that TCP leads to reductions in the likelihood of treatment, and that interventions that can increase platelet counts up to 70,000/mm^3 will act to increase the likelihood that any patient will be considered for initiation of treatment.

We also observe from the physician decisions that the stage of disease plays a significant role in the decision whether to treat, with the likelihood of treatment increasing as the patient progresses to F3, and then increasing further as they reach F4 fully compensated; however, it then declines significantly once patients experience decompensation. The model also suggests that across the four countries under consideration the probability of treating those with genotype 2 is significantly greater than treating those with genotype 1 or 3.

There are other patient factors which have not been found to have a statistically significant impact on the choices physicians made in the choice experiment; these include gender, availability of social support networks, and comorbidities. This does not mean that such effects may not exist, but that we have not been able to identify them within the sample available; this suggests that any influence they may have would be small.

We also observe that the decision whether to treat varies significantly between countries; independent of the characteristics of the patient being presented for treatment. The model shows that the physicians in France were most willing to treat the patients presented in the choice task, followed by the physicians in the UK. There was little difference in the willingness to treat between the physicians in Italy and in Spain.

6.6.2 Models of the decision to continue treatment

The second experiment, looking at the decision to continue treatment, included all of the patient-related factors considered in the first experiment, which looked at the decision to commence treatment. However, very few of these were found to play a significant role in deciding whether to continue treatment. Generally, if a patient had previously been accepted for treatment by a physician the data suggest that the physician did not then subsequently discriminate on the basis of the characteristics of the specific patient when deciding whether to continue treatment. The only factors that he or she took into account from the baseline decision whether to treat were those associated with their blood tests – the haemoglobin, platelet and white cell counts. No weight was placed on the socio-demographic or background characteristics of the patients.

We observe from the models that a patient is less likely to be kept in treatment as time elapses, and if they do not have an appropriate RNA response. The model also shows that while the baseline blood characteristics play a significant role, an improvement in any of these since treatment initiation did not increase the probability of the physicians saying they would continue treatment. However, a deterioration in haemoglobin, platelet or white cell counts from baseline were seen as a significant determinant in the decisions to either decrease dosage or to cease treatment.

Alongside the consideration of the patient's physiological response, it is clear that physicians also place a high weight on whether the patient is reliable in their adherence to treatment. However, it is interesting to note that physicians did not make decisions to decrease dosage or cease treatment on the basis of treatment side-effects; it therefore seems likely that the physicians took the patient's adherence as an indicator as to the extent to which the side-effects could be tolerated.

It can also be seen that there are differences in propensity to both cease treatment and decrease dosage by country; the likelihood of decreasing treatment is smallest in France and largest in Spain. In contrast, the likelihood of ceasing treatment is smallest in Spain (closely followed by the UK) and largest in Italy.

There are also some physician-related characteristics that affect the propensity to continue, decrease or cease treatment, independent of the progress made by the patient. Those physicians who stated that they have overall responsibility for HCV patient care in their unit were more likely to say they would cease treatment than those who did not have overall responsibility within their unit. Those who stated they make decisions by consulting colleagues were less likely to indicate in the choice experiments that they would decrease dosage. We also see that the way in which physicians perceived the healthcare system within which they were working also had some effects. Those who rated their healthcare system as very good at identifying patients at risk of HCV were more likely to continue treating patients, as were those who felt that their healthcare system was very good at managing non-attenders and those with chaotic lifestyles.

6.6.3 Using the models for forecasting impacts of interventions

The output from each model is a set of coefficients that indicate the influence that each factor has on the likelihood of treating a patient and continuing treatment. However, the magnitude of the influence of these, and how they work in combination in influencing treatment decisions, is not immediately obvious from an examination of the coefficients alone. We have therefore also programmed the models within an Excel interface to allow an exploration of the differences in probability of treatment across the range of patient profiles covered by the experiments that have been undertaken. By evaluating a range of patient profiles it is possible to observe the marginal impact that each factor may have on the probability of treatment, and thereby assess the potential impact of interventions that may seek to improve particular aspects of the patients either seeking or receiving treatment. This reveals that interventions that may, for example, influence the platelet count of patients can have significant impacts on the probability of treatment across a range of patient profiles.

While the outputs of this study are models of the probability of treating different patient profiles, the application of these could be extended to population estimates if combined

with good quality epidemiological data that could define the profile of patients being identified with HCV in a country. This would allow a country-level quantification of the impact of different interventions, whether by improving the attractiveness of patients presenting for treatment through supporting services that may assist in addressing substance dependency or by raising patient motivation prior to treatment, through to pharmacological interventions that may boost haemoglobin, platelet or white cell counts

CHAPTER 7

Using scenario building to explore future potential situations

To inform the design of the scenarios, a one-day workshop was held with the RAND Europe and Baird's CMC project team, the GSK project team, and experts from the different European countries which were the focus of this study.

The workshop aimed to serve three main purposes:

- to examine and validate the results of the qualitative and quantitative interviews, conducted in Tasks 2 and 4 (see Figure 2.1); during this part of the workshop we presented key findings from all parts of the study, discussed the methodology and received feedback on how they compared with the attendees' experiences and what was perceived as the most interesting aspects of the study
- to examine how treatment decisions would develop in future scenarios, on the basis of changes in pharmacological treatment for HCV and TCP and changes in health and social care (e.g. new treatments, better diagnosis, regulatory change and behavioural change)
- to discuss shaping actions that could be taken to improve treatment prospects and patient outcomes given current treatment regimes and clinical, policy and innovation environments, as well as social and demographic trends.

A scenario can be described as a *coherent* picture of a *plausible* future. Scenarios are used to deal with the uncertainty about what the future could bring. A scenario in the policy analysis world can be a preferred future, an unpreferred future, or just a possible future – as long as it is plausible. Non-normative scenarios are often generated in sets that give a picture of a range of plausible futures. They extend the analysis of the current situation and help identify trends using four basic elements (critical certainties and uncertainties, policy levers, relations among these elements and the (re)actions of key stakeholders, and concrete outcome indicators). Scenarios deliberately accentuate differences in these factors, taking into account the relations among them. This sharpens awareness of the role of different factors and the robustness of conclusions, while retaining the essential aspects of the complexities of the sector and associated emergent behaviour. In this sense, they can serve as an innovative platform for continuing validation of the findings, and further development to make the findings relevant and tangible for vested stakeholders.

7.1 Discussing significant factors

The development of formal scenarios began with developing an understanding of the impact of different patient characteristics on the decision to commence or continue treatment, and determining the "ability" that physicians, policymakers or pharmaceutical companies may have to change each characteristic. To achieve this, the results from the discrete choice experiment were mapped in a matrix indicating the importance placed on a factor in the decision to commence and continue treatment and the ability to alter the effect of that factor (Figure 7.1). These factors constitute the list of validated and agreed characteristics of current treatment regimes and a shared understanding of the key drivers of change generated by the team through an internal workshop, and to be discussed with external stakeholders in the expert workshop.

The workshop discussion focused on the actions required to change these characteristics, and what this would mean for the wider system and the way different characteristics might interact in order to influence treatment decisions. In other words, which characteristics independently would still have a high impact, such as platelet count, regardless of the wider system, and which characteristics were more dependent on other variables, internal and external to the patient or their provider, such as living arrangements.

The output of this initial discussion was an understanding of which characteristics will be highly uncertain in future scenarios and which will be more certain and therefore more within our control. In addition, our discussion also highlighted the variables that affect the relative level of uncertainty and what shaping actions might be taken to further influence this and thus inform our thinking about how we might move towards elements of one scenario over another. These were fed into the scenario design (Section 7.2).

Figure 7.1 The impact of patient characteristics on the decision to commence or continue HCV treatment

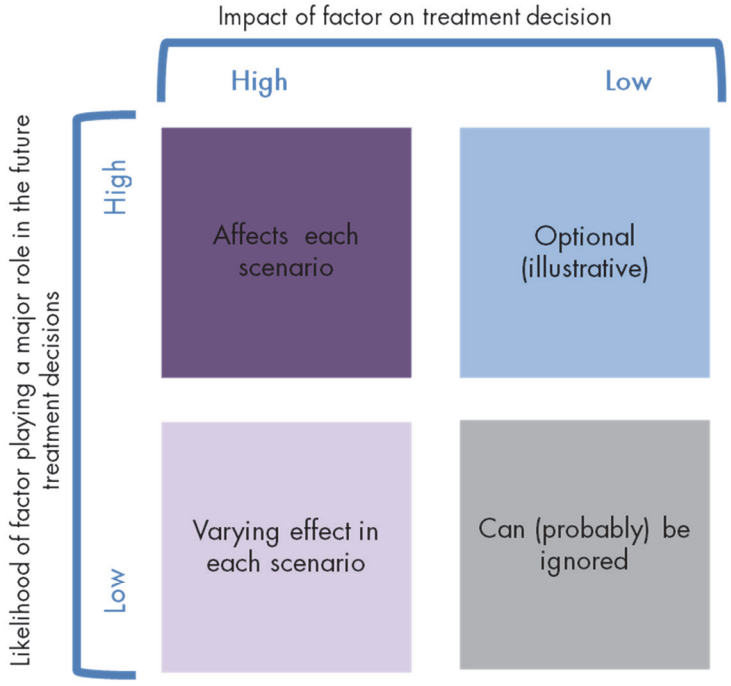
ability to change		*Impact of patient characteristic on decision to commence treatment*		
		Insignificant	**Low impact**	**High impact**
	Can change	Family support	White cell count	BMI (if obese class II)
			BMI (unless obese class II)	Living arrangements
				Patient's motivation
				Haemoglobin
				Platelet count
	Difficult or impossible to change	Gender		History of drug or alcohol misuse
		Other comorbidities	Dependants	Psychological disorders
				Country
				Age
				Stage of disease
				HCV genotype

ability to change		*Impact of patient characteristic on decision to continue treatment*		
		Insignificant	**Low impact**	**High impact**
	Can change	BMI		Haemoglobin decrease
		Living arrangements		Platelet count decrease
		Family support		White cell count decrease
		Patient's motivation		Patient's adherence
		Severity of side-effects		Physician has overall responsibility for HCV patient care in unit
				Physician makes decisions about changing treatment through informal discussions with colleagues
	Difficult or impossible to change	Gender		Response to treatment
		Age		Country
		History of drug or alcohol misuse		Physician rates healthcare system as very good for identification and testing of patients at risk of HCV infection
		Dependants		Physician rates healthcare system as very good for ability to manage non-attenders and those with chaotic lifestyles
		HCV genotype		Haemoglobin at initiation
		Stage of disease		Platelet count at initiation
		Psychological disorders		Weeks under treatment
		White cell count at initiation		
		Other comorbidities		

7.2 Building scenarios

Further to the workshop, the RAND Europe team looked at the impact of patient characteristics versus their likely role in future treatment decisions thus allowing us to populate the second type of scenario matrix (Figure 7.2), where we determined the relative position of each characteristic, from which the scenarios are built. We used a systematic approach in populating this matrix. Once key factors are identified, they are clustered based on their level of impact (the functioning of the policy area) and level of uncertainty (the direction in which they would develop and what their consequences on the policy area would be). Figure 7.2 indicates the purpose of the clustering. Factors that have a *large impact* on the functioning of the system are the most relevant for the scenario development effort (the others can be ignored). The factors with a large impact and a *low level of uncertainty* should remain constant among the scenarios – they are relatively stable assumptions about the future. The factors with a large impact and a *high level of uncertainty* are the core of the scenario development effort; they drive the differences among the scenarios. By varying these factors, a set of scenarios can be composed.

Figure 7.2 Scenario building blocks



We focused on factors which have a high impact and a high likelihood of playing a major role in future treatment decisions as these will be *similar* in each scenario, as well as factors with a high impact, but a low likelihood, which will be *different* in each scenario. These are the "building blocks" of formal scenario analysis; and are listed below:

- living arrangements (at the initiation stage)
- bloods counts (at the initiation and continuation stage)
- severe psychological issues (at initiation)
- genotype (at initiation)

- patient motivation (at the initiation stage) and adherence (at the continuation stage)
- collaboration within the healthcare system (at both initiation and continuation stage).

Finally, coherent narratives were developed around each of these scenarios to assist in understanding not only the actions required to arrive at any of these scenarios, but also the actions which might be taken *within* each scenario were it to be realised.

7.2.1 Certainties: main elements of context, common to all scenarios

Within the scenarios there were certain elements which we predicted would be present in 2020:

- At the workshop there was a general consensus that there will be an interferon-free treatment available as a single pill as there are currently several new drugs in phase 3 clinical trials (Boehringer Ingelheim, 2013).
- In addition, throughout Europe there is an ageing patient population, which will exacerbate the issues around treatment age in the guidelines and in practice. Patient population ageing will be exacerbated by the fact that, with the exception of Scotland and Wales, the countries focused on in this study are not using an eradication strategy. Therefore, those who are not treated currently for HCV will have more advanced stages of HCV in the future.
- New diagnostic tools, such as the fibroscan, will enable diagnosis to take place without an invasive biopsy most of the time. Therefore diagnosis could occur earlier and more often outside the hospital.
- Despite these improvements in diagnosis and treatment, our experts recognised it would still be difficult to reach certain populations, for example those with chaotic lifestyles, such as drug users, and migrants, where culture can lead to stigma.

7.2.2 Uncertainties

As well as certainties, there are a number of uncertainties around the future scenarios we developed, which can be broadly categorised under three main headings: treatment related, economic related, and health and social care delivery related:

- It is unknown how extensively the new interferon-free treatment will be applied. This could be dependent on its suitability for patient profiles but also on the way it is administered or on the side-effects it may have.
- The consequences of the economic crisis on health system funding streams and resources are unknown. For example, how will resources be distributed; what and who will be prioritised?
- Finally there are uncertainties around the delivery of health and social care in the future. For example, what restrictions will be placed by authorities on usage of particular treatments based on cost? Who will be authorised to prescribe treatment? This could be limited to hepatologists or extended to include infectious

disease specialists or even a wider category of physicians, such as primary care physicians. It is also unknown how the new treatment and appropriate care delivery will affect the patient profile, and vice versa (e.g. interactions between health and social care system).

7.3 Scenarios

The scenarios were developed around the different models of care delivery: community primary care, care delivered in a network of specialist practices, and highly specialised centre-based care.[28] These are described in more detail below.

7.3.1 Scenario 1: community care targeted at hard to reach population groups

In this scenario treatment is taken to those who need it, with an emphasis on community interventions to increase access for difficult to reach populations such as drug users, and to increase engagement to maximise adherence and therefore success in treatment. This enables an eradication and prevention strategy to be carried out, focusing on the hardest to reach populations and those that cause the further spread of the disease. The aim of this targeted treatment is not only to treat current cases effectively but to limit the number of new cases of infection.

The organisation of this system would be a strong community network of primary care physicians, nurses and patient associations to help with living arrangements, drug and alcohol dependency, and would provide more general social support. Peer support workers, either funded or voluntary, could be engaged to provide extra support in prevention (participating in awareness campaigns) and during treatment (e.g. helping patients under treatment to cope with side-effects). A good relationship between the health and social care sectors would be essential to the success of this trans-disciplinary approach.

Allocation of resources would be handled at a local level, with local social and health care commissioners involved in treatment and care purchasing. This local approach to the distribution of resources would inform decisionmaking about whether and how to treat on a local level.

This scenario requires several strands of education to ensure the process is successful:

- Anti-stigma campaigns to assess and address cultural barriers would be required to gain access and acceptance from populations (e.g. South Asian populations among whom the HCV stigma constitutes a real barrier to treatment).
- Capacity building for peer workers would be key to the effectiveness of their role.
- GPs and nurses would require additional training as they would be responsible for treatment delivery after full diagnosis has been given in specialised care.

[28] In these scenarios, we assume although the new drug is available it won't be suitable for everyone. For example, some genotypes will still require double or triple therapy.

In this scenario, with the push for eradication and the focus on treatment as a prevention strategy, there would be a large increase in diagnosed cases initially. The risk is that this could be too resource intensive for the health system to manage. However, in the longer term, there would be fewer patients with HCV and the potential possibility of total eradication, perhaps providing a cost-effective justification for the initial expenditure.

7.3.2 Scenario 2: care delivered in a network of specialist practices

The second scenario revolves around a network of physicians from different specialties delivering care in specialist care practices outside the hospital. It requires effective collaboration across clinical specialties to deliver holistic patient-centred care. This personalised and comprehensive approach to care increases adherence to treatment, preventing patients from dropping out and ensuring good care continuity.

The system would be organised through a strong network of specialist physicians with established collaborative working relationships. Specialties may include gastroenterology, hepatology, psychiatry, dermatology, infectious diseases and so on. Physicians would in turn be supported by specialised nurses who deliver treatment and serve as the patient's main point of contact with the health system. Pharmacists and patient associations would complement the network, by providing links into the community. Care is a multidisciplinary and integrated process.

There is an active involvement of pharmaceutical companies and other private sector players in this scenario. They provide incentives to prescribe treatment in specialist practice settings through direct agreement with the specialist physician or the network. As physicians within a network are primarily responsible for the network resources and expenditure, allocation of resources is delocalised and driven by the private sector, which competes for market shares.

Despite relying heavily on specialist nurses and physicians, this scenario still requires GP education, as GPs would be expected to provide specialists with new cases because initial diagnosis may still occur in primary care settings in countries where primary care "gate-keeping" is in place.

The main risk in this scenario is the potential competition arising between practice-based care and hospital-based specialised care, which might be detrimental to patients with more complex needs. Considering the lack of integration between the different levels of the healthcare system, it may also be more difficult to communicate effectively, spread knowledge and manage data, as there is no vertical integration or hierarchy between providers.

7.3.3 Scenario 3: highly specialised centre-based care

The third scenario envisages that treatment and care would be delivered in highly specialised centres. The focus would be on the high quality of care and ongoing innovation to treat patients in an expert and safe environment.

There would only be a few highly specialised centres around each country which could deliver the latest and most expensive treatments. In this scenario, the patient journey would become seamless, with reduced waiting times and better follow-up systems, as the use of new treatments and diagnostic tools would be less resource intensive for workforce and infrastructures. The continuity of care would improve as well, thanks to the supply of

one-to-one support with specialised nurses. Intra-disciplinarity within the hospital site would prevail, and specialists communicate well (e.g. virologists and hepatologists).

These highly specialised centres would be funded mainly by national governmental institutions and considered as flagships worth investing into. They combine forward thinking, research and excellence in treatment innovation. Additional funding may be brought by pharmaceutical companies interested in furthering research within a particular area and wanting to place their drugs on the market.

In this scenario, it is necessary to work on patient motivation and adherence as the healthcare system does not automatically make the link with social care, and patients must be ready to undertake heavy treatment. This scenario also still requires GP education: they are expected to provide specialists with new cases, as initial diagnosis may still occur in primary care in countries where primary care gate-keeping is in place.

Because there are not many centres, population coverage is not optimal and there's a risk that even fewer patients would be treated, for reasons of availability (there would be a limited number of appointments available) and access (patients would need to organise their own transport and to travel longer distances as care would not be delivered in their community). This could impact specifically on those high risk populations, such as drug users with chaotic lifestyles. The lack of focus on prevention may mean that we never move closer to eradication.

7.4 How factors which are significant now will interact in the different scenarios

Each of these scenarios has different effects on the state of the factors which we know from the discrete choice experiment have a significant role in influencing physicians' decisions (as detailed in Figure 7.1). These effects are described below.

7.4.1 Living arrangements

Living arrangements are recognised currently to be a factor which has a high impact on the decision to commence treatment, and is able to be changed. Although, once treatment has commenced, living arrangements do not have an impact on the decision to continue treatment.

In Scenario 1, this would become less of a problem as the system would include local initiatives (funded by local governments or NGOs) to assist patients in finding suitable accommodation while undergoing treatment or to provide a safe place for treatment delivery. However, it is still an issue in the other scenarios as both systems are still physician oriented and might lack links with the community or social care, in scenarios 2 and 3 respectively.

7.4.2 Blood counts

Blood counts are currently a factor influencing both initiation and continuation of treatment. The levels of haemoglobin and platelet counts are instrumental in the decision to initiate treatment and a decrease in haemoglobin, platelet or white blood cell count has a high impact on the decision to continue treatment. One of the drivers for this factor is that it is not always easy for physicians to monitor patients while they are on treatment. Given this, the factor will still be an issue in the future in Scenario 1, where the less

specialised environment may result in a less systematic monitoring of blood counts and the available solutions to address low blood count may be more limited, despite the introduction of new treatments. However, this issue is no longer a limitation in scenarios 2 and 3, because of the close monitoring that would occur, linked with the expertise of colleagues from other specialties and the introduction of new medical treatments to manage blood counts more effectively.

7.4.3 Psychological issues

Psychological issues in the patient were defined as a factor that had a high impact on the decision to initiate treatment but we recognise that these are difficult to change. However, these issues were not proven to have an impact on the decision to continue once treatment had commenced. In the scenarios presented, all futures would be an improvement on the current situation. For example in Scenario 1, where the condition was manageable, local initiatives, funded by local governments or NGOs, would be available to assist patients in sourcing suitable psychological support. In addition, with a prevention-based approach, such as that in Scenario 1, there is the potential for "spillover" improvements to reduce the number of patients who suffer from psychological problems in the first place (because there is a more integrated healthcare system in place). Psychological issues are managed in scenarios 2 and 3 by close monitoring of patients. This is achieved through the presence of psychiatrists who would be able to treat those with more severe psychosis effectively and through the use of new HCV drugs with fewer side-effects.

7.4.4 Genotype

The genotype of the patient has a high impact on a physician's decision to commence but not to continue treatment. This is because some genotypes respond better than others to the currently available treatments. In the scenarios described above, this would still be an issue in the community-based care environment (Scenario 1) and difficult to treat genotypes may need to be referred to more specialist care. However, this is less likely to be a limiting factor in treatment in the outpatient and hospital settings (scenarios 2 and 3), as there is likely to be someone with the experience and relevant disciplinary knowledge to deal with such cases in these scenarios.

7.4.5 Patient motivation and adherence

The patient's perceived motivation has a high impact on the decision to initiate treatment. Once under treatment, the patient's adherence to the regime also has a high impact on the decision by physicians to continue treatment. In the scenarios, we foresee that adherence will not hinder treatment as significantly as at present, but initial motivation may still be an issue. In Scenario 1, the strong social network and peer support would help patients, where required, to become and remain motivated and to support them in understanding the treatment and its effects. In Scenario 2, the presence of specialised nurses and the availability of a network of physicians would support individuals to ensure adherence to the treatment. However, motivation to initiate treatment could still be an issue in this scenario. This could be further exacerbated by the care setting, which could leave patients feeling isolated as there may not be similar cases around them, as present in the other two settings. In Scenario 3, treatment adherence would be improved by the presence of specialised nurses and the use of new drugs with fewer side-effects. However, without the peer network that the community-based environment offers, motivation to initiate treatment may remain an issue.

7.4.6 Collaboration within the healthcare system

HCV is a complex disease and often requires input from multiple specialists and sectors, including psychiatric or social support as a result of the patient's circumstances or some common comorbidities, such as HIV or diabetes. It is essential that the healthcare system collaborates to ensure that the patient receives holistic care. In each system, different types of collaboration would ensure that there is communication and partnership between healthcare professionals and others involved in care delivery. Scenario 1 provides trans-disciplinary collaboration between the healthcare, social care and voluntary sectors. Scenario 2 is a horizontal multidisciplinary collaboration within the healthcare system and the network of specialist practices. Scenario 3 demonstrates an interdisciplinary collaboration within an individual centre where experts can be brought from different departments in the institution without barriers. All of these systems aim to increase collaboration through their different settings.

7.5 Conclusions and next steps

The scenarios-based futures thinking presented here enables the differentiation and analysis of the impact of changes in health systems as opposed to changes at the level of clinicians' behaviours and attitudes. Thus, depending on the type of system adopted in the future, there will be different challenges and different factors will be emphasised. The narratives and analysis presented here can be used as a guide to inform future strategic decisions which might be taken in order to either help situate oneself within any of the given scenarios and make plans, or to help take an active role in shaping different scenarios which might come to light in the future. We suggest below some examples of shaping actions addressing some of the relevant factors among clinical, lifestyle and healthcare-system-related characteristics:

Clinical: Current barriers to commencing treatment include levels of platelets and red and white blood cells. These factors continue to be an issue when deciding whether to continue treatment. Therefore the development of treatments which alleviate these issues would increase the number of patients who could commence and continue treatment. The issue of genotype could also be addressed if a new drug compatible with all forms of the disease were developed. Progress is constantly being made in this field and therefore shaping actions need also to take into account changes, such as the inevitable launch of an interferon-free treatment.

Lifestyle: The main lifestyle factors which were identified as impacting on the decision to initiate treatment were living arrangements, motivation, and a history of alcohol and substance misuse. Living arrangements were consistently highlighted as an issue, because of the current need to refrigerate medication. However, such concerns may be alleviated with the move towards an oral pill, rather than an injection. All of these factors require coordinated interaction with other parts of the health and social care systems, and with the voluntary sector (e.g. patient associations). Support from psychiatrists throughout therapy could help patients with adherence issues, those with chaotic lifestyles, or those with current or previous alcohol or substance misuse.

Healthcare system: From the results of the discrete choice experiment we see that there are major differences in physicians' propensity to treat (both to initiate and to continue) across

countries. It seems highly likely that available resources and system organisation play a role in influencing these decisions, e.g. the eradication campaign in Scotland has probably contributed to higher treatment rates, while the current funding constraints in Italy may have contributed to a lower willingness to treat.

Interventions seeking to reshape elements of care within healthcare systems do not necessarily have to be targeted at the physicians making the treatment decisions. For example, improving the process and support for patients entering and within the system could both increase adherence, and also improve physicians' confidence in the system, which from our results would lead to an increase in treatment continuation.

A further system improvement may be obtained by identifying steps to facilitate the updating of guidelines to reflect best practice. For example, the use of certain drugs, such as eltrombopag or EPO to alleviate complications (low blood counts and haemoglobin levels), could help lead to more patients fulfilling the criteria that physicians required to undertake treatment.

CHAPTER 8 Conclusions

8.1 Factors important in influencing physicians' decisions

Within this study we used a multi-method approach to identify a number of factors that were found to be important in affecting physicians' decisions to commence HCV treatment for patients. These are summarised in Table 8.1.

Table 8.1 The importance of factors influencing physicians' decisions on HCV treatment

Factors	Literature review	Key informant interviews	Discrete choice experiment
Age			
BMI			
Comorbidities			
Country			
Dependants			
Family support			
Gender			
Genotype			
Haemoglobin levels			
History of alcohol or substance misuse			
Living arrangements			
Patient motivation			
Platelet count			
Psychological disorders			
Stage of disease			
White blood cell levels			

KEY: Dark – high impact, Light – low impact, Clear – insignificant impact[29]

These factors include patient characteristics (clinical and lifestyle factors that constitute the patient profile) and healthcare-related factors (organisational or system-related factors). As

[29] Please note that those categories correspond to a qualitative assessment rather than quantitative measure of importance and significance, except for the discrete choice experiment where the assessment is based on the quantitative findings.

Table 8.1 shows, there are some variations in the range of factors that were identified in the different methods. The literature review highlighted the importance of gender, for instance, which was not verified by the interviews or the discrete choice experiment. It implies that while gender has a proven influence on the response to treatment, physicians do not base their decisions as to whether to treat on this factor and treat men and women in the same way. Another example is the comorbidities: comorbidity issues constituted a good share of the literature, and interviewees expressed concerns about treatment of patients with comorbidities, but this factor was not significant in the discrete choice experiment. This discrepancy probably arises because the comorbidities selected for the discrete choice experiment (e.g. HIV, diabetes and renal disease) were the most common and therefore not considered as strong barriers to treatment by physicians, while in the literature review and the interviews the most problematic or less common comorbidities (e.g. epilepsy, auto-immune diseases, sarcoidosis) were also reported on. On the other hand, only the discrete choice experiment picked up the relevance of BMI (when at the severely obese level) for treatment initiation, which might suggest a need to produce more research and better guidelines on the treatment of obese patients.

Interestingly, the factors involved in continuing treatment often differed from those influencing the initiation of treatment. At the continuation stage, the specific patient profile and the patient's situation were no longer important factors and the decision focused on the clinical response to the treatment. For example, significant factors include the duration of the treatment so far, the patient's adherence to therapy, and a reduction in haemoglobin, white blood cell and platelet counts. Although severe side-effects were mentioned in the key informant interviews as a factor influencing the decision to continue treatment, this was not reflected in the discrete choice experiment results.

8.2 Focus on the impact of TCP on treatment decisions

A subset of the literature review focused on haematological abnormalities, such as TCP (Section 3.2.1). Platelet count was identified as an important factor in influencing the decision to treat and a number of studies focus on agents which can increase platelet counts in patients in order to ensure they are eligible for antiviral HCV therapy. In the key informant interviews, TCP was mentioned as an important haematological factor influencing treatment decisions to initiate and continue treatment in Italy, Spain and the UK. Interviewees in Italy and the UK mentioned issues with the guidelines around the treatment of patients with low platelet counts, stating that the threshold levels were too high compared with reality. Interviewees' views on the importance of TCP varied across countries; French interviewees stated that it was rare to modify treatment based on TCP.

The models estimated from the data collected through the discrete choice experiments provide further insight and allow us to quantify the relative importance placed on TCP alongside other patient characteristics in decisions on initiating treatment and continuing treatment should TCP occur during the course of treatment. Using the model it is possible to examine a range of different patient profiles and for each to look at the difference that having, or not having, TCP has on the patient's probability of receiving treatment. This can be used to illustrate the possible impact that may be achieved with new therapies that could reduce the onset of TCP.

8.3 Relative importance of factors

The models from the discrete choice experiments provide a quantification of the relative weight placed on a range of different patient-related factors, along with insight into how these differ by country. The implemented models provide forecasts of the probability that different profiles of patients would be treated, based on the decisions that physicians had indicated that they would make when asked in the survey. By varying the different patient characteristics it is possible to gain insight into the relative influence that each factor has when deciding whether a patient should be treated.

While the model illustrates the influence that each of these has on treatment decisions independent of each other, we know that in actual patients some of these factors are interrelated and that a change in one factor may also lead to a change in another. In interpreting the findings it is therefore important to take this into account, if considering how interventions may seek to influence these factors to improve the probability that certain patient groups will be judged as eligible or appropriate for treatment.

In order to validate the relationship between factors and assess their future impact on treatment decisions we explored the emerging findings with a workshop of experts and developed a set of scenarios. In the scenario building, blood counts, genotype, patient commitment (motivation at initiation and adherence at continuation), living arrangements, severe psychological issues, and collaboration within the healthcare system were considered as factors that may have a high impact on treatment decision, but whose impact could be decreased by appropriate interventions, including investment into new drug development, public health education campaigns and so on.

8.4 Policy implications

This study has identified a range of factors that influence the physicians' treatment decisions on HCV infected patients, and quantified the relative influence of each. It provides a better understanding of the reasons that motivate the initiation and continuation of treatment, and the barriers that hinder them.

Overall there are three types of factors which influence treatment decisions: healthcare-system-related, clinical and lifestyle factors. This study shows that all of these play a role in influencing the complex process of physicians' decisionmaking. In order to alter the situation for the future, various shaping actions have been suggested to support change.

Shaping actions could include addressing clinical barriers to treatment (such as blood counts levels and genotype) by investing in the development of treatments with fewer side-effects and better efficacy, which would alleviate these issues and increase the number of patients who could commence and continue treatment. Progress is constantly being made in this field and therefore shaping actions need also to take into account changes, such as the inevitable launch of an interferon-free treatment.

The main lifestyle factors could be addressed by improving the collaboration within the health system, across the health and social care systems, and with the voluntary sector (e.g. patient associations). Support from psychiatrists throughout therapy could help patients

with adherence issues, those with chaotic lifestyles, or those with current or previous alcohol or substance misuse.

In light of the importance of the motivation and adherence factors, it seems important to stress that this study focused solely on the factors that influence the decisions of healthcare professionals. However, as our study shows that the patient is also heavily involved in the treatment decision, a complementary piece of work could be to conduct a similar study to understand the patient's perspective on what factors influence their decision to present for treatment or not, and once under way whether to continue treatment or stop it.

As available resources in the health system and system organisation play a role in influencing these decisions, interventions seeking to reshape elements of care within healthcare systems (e.g. improving the patient journey, increasing support from specialised nurses) could both increase adherence and improve physicians' confidence in the system, which our results suggest would lead to an increase in treatment continuation. A further system improvement may be obtained by identifying steps to facilitate the updating of guidelines to reflect best practice. For example, the use of certain drugs, such as eltrombopag or EPO to alleviate complications (low blood counts and low haemoglobin levels), could help lead to more patients fulfilling the criteria that physicians require to undertake treatment.

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APPENDICES

Appendix A: Literature review search strategy

Country (probably to be used as mesh terms)	"Europe" OR "European" OR "EU" OR "Italy" OR "France" OR "Germany" OR "United Kingdom" OR "UK" OR "Britain" OR "England" OR "French" OR "German" OR "British" OR "English" OR "Italian" OR "Welsh" OR "Scottish" OR "Spain" OR "Spanish"
Disease	"Hep C" OR "hepatitis C" OR "HCV" OR "hepacivirus"
Treatment	"treatment" OR "dosage" OR "drug" OR "care" OR "therapy" OR "chronic" OR "PEG IFN/RBV" OR "boceprevir" OR "telaprevir" OR "antiviral" OR "thrombopoietin" OR "interferon" OR "ribavarin" OR "Revolade" OR "eltrombopag"
User profile – related conditions	"thrombocytopenia" OR "TCP" OR "platelet" OR "infection" OR "stage" OR "viral" OR "genotype" OR "Hepatitis B" OR "coronary disease" OR "HIV" OR "cirrhosis" OR "liver" OR "sustained viral response" OR "SVR" OR "side effect" OR "comorbidity" OR "co-infection"
User profile – non-medical characteristics	"age" OR "gender" OR "ethnicity" OR "race" OR "socio-economic" OR "immigrant" OR "marginalised" OR "vulnerable" OR "income" OR "preference" OR "choice" OR "concordance" OR "adherence" OR "adherence" OR "alcohol" OR "drug" OR "substance abuse" OR "substance misuse" OR "relapse" OR "risk profile" OR "risk behaviour" OR "risk behavior" OR "response" OR "unresponsive"
Health system factors – finance, payment, reimbursement	financ OR resource OR fund OR cost OR insur OR reimburse OR organisation OR organization OR environment OR pay OR insurance OR insured OR payment OR fee
Health system factors – regulation	practice guidelines OR guideline OR guideline adherence OR clinical protocol OR critical pathway OR physicians practice patterns OR guidance OR standard OR referral pathway OR waiting time OR prescription
Health system factors – organisation	public OR private OR acute OR social OR centralised OR decentralised
Health system factors	health care quality OR access OR referral OR standards OR coverage OR eligibility
Decisionmaking – care regime	"combination" OR "adjust" OR "terminat" OR "stop" OR "end" OR "start" OR "change" OR "adapt" OR "continu" OR "mental" OR "physical" OR "haematological" OR "initiat"
Decisionmaking – provider's characteristics	"Time" OR "time management" OR "time factors" OR "workload" "decid-" OR "choos-" OR "physician" OR "doctor" OR "clinician" OR "provider" OR "nurse" OR "specialist" OR "experience" OR "expertise" OR "barrier- or constrain- or obstacle- OR disincentive- OR "impede" OR "clinical"

Appendix B: Internal key informant interview guide (for interviewer)

Background to project

RAND Europe has been commissioned by GSK to conduct a study which aims to better understand the range of factors that may influence physicians' decisionmaking on HCV treatment. These may include clinical, social and behavioural, and demographic factors as well as those related to physician experience, or the health and social care systems more broadly (regulation, financing). It seeks to investigate the comparative influence and importance of specific factors and combinations of factors, and the trade-offs implicated in the decisionmaking process, for example, whether to commence or terminate a given treatment or adjust dosage and duration of treatment. As part of this project we seek to undertake interviews with key experts from the UK, France, Spain and Italy to provide further insights into the more salient issues around decisionmaking that are not easily accessible from the published literature. We seek to for experts to represent a range of stakeholder views: (i) academics; (ii) clinicians and other healthcare professionals; (iii) policymakers/regulators; (iv) civil society (patient associations, charities, NGOs, advocacy groups). Interviews aim to explore experts views and experiences.

Interviews will be carried out as telephone interviews, lasting approximately 45 minutes. We will seek consent from interviewees to audio record interviews. Taking part in the interview is entirely voluntary and experts will be given the opportunity to withdraw at any time without having to give a reason. All information collected about the interviewee and their organisation during the course of the interview will be kept strictly confidential. Transcripts of the interviews will be made available only to the investigators and will be kept in a secured file.

Other preliminary comments and guidance for interviewer

- Always try to get examples, but keep time constraints in mind.
- As necessary, remind the interviewee that we are interested in insights based on their experience and knowledge and/or expert perceptions (so if they cannot relate to and answer a question that is fine).
- Remind interviewee and get recorded consent that they are ok with the interview being recorded for internal analysis purposes.

Questions

1) Just as a start, can you please tell us a little bit about your background, role and engagement in the hepatitis C field?
2) In your role, which stakeholder groups involved with hepatitis C do you work/interact with? What is the nature of this contact?
    a. Probe for involvement with *physicians/healthcare professionals* and explore what type (e.g. nurse, GP, etc); *regulators/policymakers*; *academics*; *patients*; *civil society* (advocacy groups, charities, NGOs); other; try to get examples
    b. Probe for *national, regional and international* levels of involvement
    c. Probe for *frequency* – how often with specific groups?
3) How is the overall system of care for persons with HCV infection organised and who is responsible for decisions on diagnosis and treatment, and how is this being paid for (and by whom)? More specifically:
    a. To what extent do you think that HCV detection and treatment are prioritised by policymakers?
    b. Who pays for diagnosis and treatment? Is there dedicated/ring-fenced funding for this disease area?
    c. What is the typical journey for someone with HCV infection – from diagnosis to treatment? What is the typical entry point for someone with HCV into the system (e.g. primary care)?
    d. Does the pathway differ for different population groups (e.g. substance misuse, prison, immigrants) and if so how?
    [probe not only on decision to initiate treatment, but also on patient support while being treated, management of adverse events]
    e. Do you consider the current system of diagnosing and treating persons with HCV infection in your country adequate? Please consider the perspectives of practitioners testing for/treating HCV patients and HCV patients in particular:
        - What are the main enablers?
        [probe for established referral pathways; dedicated funding streams; stigma reduction; testing available in settings that are easily accessible to those at risk, etc]
        - What are the main barriers to treatment?
        [probe for funding constraints; lack of "ownership" among practitioners of the disease; care fragmentation; stigma; etc]
    f. Has there been a change in the processes of detection, testing and treatment (especially of those at high risk) over time?
    g. What do you see as the main challenges for the healthcare system in your country if a higher proportion of the infected population was diagnosed?

[probe on resource, facility, funding implications]

[*NOTE: they might start talking about guidelines and we want to know that, but that isn't the core focus of this question – here it is about the physician and/or patient choice... to probe for that]*

[NOTE: if they say the decisionmaking in the country is decentralised/differs by region... you can focus on that]

4) From your experience, how do you think does a given "patient profile" impacts on how a practitioner will decide whether or not to initiate or continue treatment? "Profile" may include clinical profile as well as patient characteristics including behavioural, lifestyle or demographic factors. To what extent will the way decisions are made differ for different types of patients? Please provide examples where possible. Why do you think that is the case?
   [probe also role of physician experience and authority]

5) To what extent does the *process of decisionmaking* depend on the *different stages of disease progression* (e.g. decisions to initiate, adjust dosage, terminate treatment?). To what extent will factors other than clinical profile (still) influence decisions taken at each stage of the disease process?
6) How do you rate the level of implementation of:
   a. national guidelines
   b. European Association for the Study of the Liver (EASL, 2011) guidelines
7) What are the main challenges to guideline implementation and adherence?
   [probe for factors such as organisational, e.g. lack of infrastructure/equipment; financial, e.g. lack of funding; behavioural, e.g. lack of belief in appropriateness of guidelines]
8) Based on your knowledge/experience, to what extent does the diagnostic and treatment pattern for HCV patients in your country differ from practice in other European countries and internationally (e.g. US)? If so, how? Any examples? Why do you think that is the case?
9) To what extent are low platelet count associated factors (e.g. thrombocytopenia) taken into account in decisions about initiating, adjusting dosage or terminating treatment with the current standard of care (PEF IFN/RBV[30])? Can you elaborate?
10) What is your view on the relative importance of different factors on decisionmaking about diagnosis and treatment of HCV infection? For example, as they relate to the information Table B.1.

[30] Stands for the well-accepted standard of care treatment: pegylated-interferon and ribavirin combination therapy.

Table B.1 Interviewees' perceptions on the relative importance of different factors on decisionmaking in the diagnosis and treatment of HCV[31]

Factors influencing decisionmaking: categories	Examples by category	Which specific factors do you consider as particularly important in practice for those making decisions on treatment?
Clinical	e.g. haematological abnormalities, thrombocytopenia, anaemia, neutropenia, viral genotype	
Related conditions and comorbidity	e.g. depression, HIV, hepatitis B, coronary disease, cirrhosis, non-HCV-related liver disease, diabetes, weight, renal disorders, depression, epilepsy, uncontrolled autoimmune diseases, contraindications associated with pregnancy, other	
Side-effects experienced by patient as a result of HCV treatment with drug	mild fatigue, depression, irritability, sleeping disorders, skin reactions and dyspnea; haematological side-effects discussed above Unusual or severe: seizures, bacterial infections, autoimmune reactions, interstitial lung disease, neuroretinitis, bone marrow aplasia or idiopathic thrombocytopenia.	
Behavioural	Substance misuse (drugs, alcohol); drug-replacement therapy; patient choice about therapy and adherence; prison	
Demographic	Age, gender, ethnicity, socioeconomic status; whether migrant	
Funding models	Finance mechanisms, insurance, payers, fees, reimbursement	
Regulation	Guidelines, standards, formal referral pathways, prescription patterns	
Health system organisation	Public or private care, centralised or decentralised decisionmaking	
Access to care	Access, eligibility, coverage, referral practices, waiting times	
Quality of care: provider characteristics	Physician, nurse, specialist; their experience, preferences, incentives, access to information, training, guideline adherence, clinical judgement	
Quality of care: patient perceptions and experiences	Patient experience and awareness; choice, dignity and respect; ratings of service provider	

[31] This table and the protocol questions were given to interviewees before the interview in a follow-up email once they had agreed to be interviewed. During the interview they were asked to identify which specific examples or sub-factors in each category were particularly important in making a decision on treatment, and to comment on any others, based on their experience or perception of their importance.

Appendix C: Profile of interviewees

Table C.1 Profile of interviewees in this study

France: - 2 academics or clinicians (professors with clinical roles in public hospitals, but also with senior roles in policy bodies) - 1 charity (senior executive at patient association, also is HCV patient) - 2 clinicians (specialist physician–hepatogastroenterologist, outpatients) - Employees of regulatory and policy bodies refused to participate because the study was funded by a pharmaceutical company Most interviewees had influence in policy circles, for example through guideline creation, development of national plans, senior roles in national policy bodies and public health authorities, various liver disease and hepatitis societies, and international advocacy in policy circles.
Italy: - 2 clinicians (1 gastroenterologist with special interest in hepatology; 1 gastroenterologist with pathology focus) - 1 academic - 1 charity (advocacy group) - 1 MP senator, commissioner of Health Care Commission and the Investigating Commission on Health Care System since 2001 Some interviewees had contact with and influence on the policy world as consultants on new HCV drug introduction, or in advocacy roles.
Spain - 2 academic clinicians (1 liver physician, 1 internal medicine physician) - 2 senior members of relevant NGOs (advocacy and counselling) - 1 policymaker of a regional government Some interviewees had influence in policy through regulatory agencies.
United Kingdom: - 1 policy maker and academic (academic but part of a health protection agency) - 1 clinician and charity worker (nursing background and currently in charity sector) - 1 clinician or academic (consultant hepatologist and academic) - 1 charity worker and patient (works in charity but is hepatitis C patient) - 1 academic Most interviewees had contact with the policy world as advisors, consultants on guideline development or representatives of patients to policymakers.

Appendix D: Workshop agenda

Hepatitis C: Understanding factors that influence the physicians' treatment decisions

Workshop: reviewing work done so far and developing future scenarios

16th January 2013 at RAND Europe, Cambridge

Agenda

10.30–10.45: Introductions by Jo Chataway, RAND Europe

10.45–11.00: Why did GSK commission this study?, Helen Smith, GSK

11.00–11.10: A brief reflection on major factors influencing treatment decisions. Group exercise facilitated by Jo Chataway

11.10–11.40: The literature review and key informant interviews. Presentation by Céline Miani, RAND Europe

11.40–12.10: The patient journey. Presentation by Catriona Manville, RAND Europe

12.10–1.00: The discrete choice experiment. Presentation by Peter Burge, RAND Europe

1.00–1.45: *Lunch and an opportunity to explore the discrete choice experiment model*

1.45–2.40: Constructing a matrix to underpin scenarios and defining scenarios. Group exercise facilitated by Molly Morgan Jones, RAND Europe

2.40–3.00: Tea Break

3.00–4.15: Further development and testing of future scenarios. Group exercise facilitated by Molly Morgan Jones, RAND Europe

4.15–4.30: Reflection on major factors influencing treatment decisions. Group exercise facilitated by Jo Chataway

4.30: Workshop ends

Appendix E: Full discrete choice experiment questionnaire

Table E.1 Attributes for Experiment 1

Category	No.	Attribute	Levels					
			1	2	3	4	5	6
Patient information	1	Gender	Male	Female				
	2	Age	30	45	60	70	80	
	3	BMI	17 kg/m^2	22 kg/m^2	28 kg/m^2	32 kg/m^2	35 kg/m^2	
	4	History of drug and/or alcohol abuse	No history of drug and/or alcohol misuse	Past history of drug and/or alcohol misuse	Ongoing drug and/or alcohol misuse, but under treatment	Ongoing drug and/or alcohol misuse, but not under treatment		
	5	Living arrangements	Patient has stable living arrangements	Patient does not have stable living arrangements				
	6	Social support network	Patient has close family support	Patient has no close family support but has support from others	Patient has no social-support network			
	7	Dependants	Patient has dependants who need support	Patient has no dependants who need support				
	8	Patient's motivation	Patient is motivated to undertake	Patient is not particularly	Patient has reservati			

			treatment	motivated to undertake treatment	ons about treatment because of cultural or ethic background			
Clinical results	9	HCV genotype	1	2	3			
	10	Stage of disease	F2	F3	F4 fully compensated	F4 mild decompensation	On the transplant list	
	11	Haemoglobin (anaemia)	<8.5g/dl	8.5–10g/dl	>10 g/dl			
	12	Platelet count	<25,000/mm^3	25,000–40,000/mm^3	40,00–60,000/mm^3	60,000–80,000/mm^3	80,000–100,000/mm^3	>100,000/mm^3
	13	White cell count	<500/mm^3	500–750/mm^3	>750/mm^3			
Comorbidities	14	Psychological disorders	No history of psychological disorders	Past history of mild depression and psychological disorders	Ongoing mild depression and psychological disorders, currently under treatment	Past history of psychosis	Ongoing episodes of psychosis, currently under treatment	
	15	Other comorbidities	None	Diabetes	HIV	Renal disease		

Table E.2 Attributes for Experiment 2

	No.	Attribute	Levels					
			1	2	3	4	5	6
	1	No. of weeks under treatment	2	4	8	12	16	20
Change in clinical results	2	Response to treatment (HCV-RNA)	Positive RNA (>2 log drop)	Positive RNA (<2 log drop)	Negative RNA			
	3	Haemoglobin (anaemia)	–1	0	1			
	4	Platelet count	–2	–1	0	+1	+2	
	5	White cells count	–1	0	1			
Adherence and side-effects	6	Patient's adherence	Patient is fully compliant with treatment	Patient is virtually fully compliant with treatment	Patient is unreliable in their adherence with treatment			
	7	Severity of side-effects	No significant side-effects to date	Minor side-effects	Strong but manageable side-effects			

Table E.3 Background questions we asked interviewees in this study

Questions	*Answers*
How old are you?	*1. 25–34* *2. 35–44* *3. 45–54* *4. 55–64* *5. 65+*
In which country do you practise?	*1. France* *2. Italy* *3. Spain* *4. UK*
What is your specialty?	*1. Gastroenterologist* *2. Hepatologist* *3. Infectious disease specialist*

	4. General practitioner *5. Doctor in hospital training post* *6. Specialist nurse*
Do you work for a…? (tick as many as needed)	*1. Private hospital/clinic* *2. Public hospital* *3. University hospital* *4. Specialised research and/or treatment unit* *5. Independent practice (primary care)* *6. Independent practice (secondary/specialist care)* *98. Other, please specify*
How many years of experience do you have since gaining your medical/nursing qualification?	
How many years of specialised care of patients with HCV infection do you have?	
Who has overall responsibility for HCV patient care in your unit?	*1. Yourself* *2. Yourself with one or two other colleagues* *3. Another clinician*
Approximately how many HCV patients being considered for treatment with pegylated alfa interferon and ribavirin do you see per year?	
Does your unit include specialist nurses as part of the HCV treatment team?	*1. Yes* *2. No*
Does your unit include links with health professionals from other specialties as part of the HCV treatment team?	*1. Yes* *2. No*
Which specialities are seen most often?	
What phrase best suggests the way you would most frequently make decisions about initiating or changing treatment for patients with hepatitis C?	*1. By myself* *2. Referring to a more senior colleague* *3. Through informal discussion with colleagues* *4. Through a more formal case conference*
Does your unit include links with other non-clinical service providers, e.g. social services, addiction services, housing agencies, etc, as part of the HCV treatment team?	*1. Yes* *2. No*
Which service providers, as part of the HCV treatment team, are seen most often? [Open text]	

Table E.4 Questions we asked interviewees in this study about the characteristics of their healthcare systems

	1	2	3	4	5
	Very poor	Poor	Neutral	Good	Very good
The patient's journey					
1. Overall access to care for patients with HCV					
2. Identification and testing of patients at risk of HCV infection					
3. Effectiveness of the referral pathway to treatment					
4. Waiting time from referral to your clinic					
5. Overall quality of care for patients with HCV once in specialist care					
6. Ability to manage non-attenders and those with chaotic lifestyles					
7. Support services for patients, e.g. access to specialist nurses					
Heath system questions					
8. What is the overall level of resources dedicated to HCV treatment?					
9. What is the level of adherence to national and European clinical practice guidelines?					
10. How effective is collaboration between specialties (e.g. collaboration between hepatologists and HIV specialists)?					
11. How effective is collaboration between the health and social care sectors?					
12. How would you rate level of access to care, and quality of care, for special population groups (homeless, drug and alcohol users, etc)?					