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# The Cost-Effectiveness of Hepatitis C treatments in Ireland: A Multi-Technology Assessment

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A thesis submitted to the University of Dublin, Trinity College, for the Degree of

Doctor in Philosophy

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**January 2016**


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# Summary

**Introduction** Chronic Hepatitis C (HCV) is an important public health concern with an estimated 20,000 to 50,000 people infected in Ireland. Horizon scanning at the National Centre for Pharmacoeconomics in 2011 identified that HCV therapeutics was likely to have a high budget impact in the coming decade. HCV treatment with pegylated interferon and ribavirin has never been assessed for cost effectiveness in the Irish setting. It was proposed to undertake a research programme to address the deficits in the knowledge base in this area, with a view to undertaking a cost-utility analysis of HCV treatment in Ireland.

**Methods** To establish national estimates of the number of patients treated for HCV in the past decade, the Primary Care Reimbursement Services dataset was interrogated for co-prescriptions of pegylated interferon and ribavirin. The cost of these prescriptions was established by applying the drug acquisition costs of the medications to the Health Service Executive (HSE). A micro-costing study was undertaken to establish the cost of ambulatory and inpatient care for patients with different degrees of liver impairment. They were categorised according to pre-specified criteria which correlated with clinical stages of disease progression. The resource utilisation of ambulatory care was established by timing outpatient reviews and combining the manpower cost with the cost of laboratory and radiology investigations undertaken. Inpatient care costs were established through interrogation of the electronic patient records of patients with end-stage liver disease and application of appropriate diagnostic related group costs to the inpatient episodes. Health related quality of life data in Irish patients with different stages of HCV was established through the administration of the generic health utility questionnaire, the EQ 5-D 5-level. A systematic review and mixed treatment comparison of randomised controlled trials of patients treated with boceprevir or telaprevir containing treatment regimens was performed in order to develop estimates of the relative efficacy of the agents. A hybrid Decision tree-Markov model was constructed in

TreeAge to investigate the cost-utility of HCV treatment in Ireland. Deterministic and probabilistic analysis was undertaken and a fully incremental analysis was performed considering three different populations. The basecase population contained 20% cirrhotic patients and 80% non-cirrhotic patients. The analysis was also run with a population who all had cirrhosis entering the model and a population with mild to moderate HCV at the start of the model. **Results** Between 2001 and 2012, 2320 patients were treated for HCV with pegylated interferon and ribavirin at a cost of €27,614,326. The annual cost of mild HCV was €398, moderate HCV €417, compensated cirrhosis €1790, decompensated cirrhosis €10,596, hepatocellular carcinoma €27,652, liver transplantation Year 1 €137,176, liver transplantation after Year 1 €5,337 and sustained virological response €83. The utility values for patients with HCV were lower than age-matched population norms and decreased with progression of liver disease. Patients with mild HCV had utility values of 0.75, moderate HCV 0.74, compensated cirrhosis 0.64, decompensated cirrhosis 0.46, hepatocellular carcinoma 0.52, liver transplantation in the first year 0.49, liver transplantation after the first year 0.59 and sustained virological response 0.81. There was no significant difference detected in the relative efficacy of boceprevir and telaprevir in a treatment naïve cohort. Telaprevir had greater relative efficacy than boceprevir in the setting of previous treatment relapse. In the basecase population, the probabilistic ICER for pegylated interferon and ribavirin versus No Treatment was €23,383/QALY, for boceprevir versus pegylated interferon and ribavirin was €34,210/QALY and for telaprevir versus boceprevir was €135,482/QALY.

**Conclusion** Treatment of HCV in Ireland with pegylated interferon and ribavirin is a cost-effective option. Treatment with either of the protease inhibitors is cost-effective when compared to pegylated interferon and ribavirin. Depending on the population under consideration, the most cost-effective protease inhibitor changes with boceprevir being preferred from a cost-effectiveness perspective in patients with mild to moderate HCV and telaprevir being preferred in patients with cirrhosis.

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# List of Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| AIDS | Autoimmune Deficiency Syndrome |
| ATC | Anatomical Therapeutic Chemical |
| BOC | Boceprevir |
| CDC | Centre for Disease Control |
| CEAC | Cost-effectiveness Acceptability Curve |
| CE plane | Cost-effectiveness plane |
| DAA | Direct Acting Antiviral |
| DES | Discrete Event Simulation |
| DPS | Drug Payment Scheme |
| DRG | Diagnostic Related Group |
| DSA | Deterministic Sensitivity Analysis |
| EASL | European Association for the Study of the Liver |
| EGFR | Epidermal Growth Factor Receptor |
| EMEA | European Medicines Agency |
| EOTR | End of Treatment Response |
| EPO | Erythropoietin |
| EQ-5D | Euroqol 5-Domain |
| ER | Endoplasmin Reticulin |
| ESLD | End Stage Liver Disease |
| EVR | Early Virological Response |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GMS | General Medical Scheme |
| GUIDE | Genitourinary Medicine and Infectious Diseases |
| HCC | Hepatocellular Carcinoma |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HRQOL | Health Related Quality of Life |
| HSE | Health Service Executive |
| HTA | Health Technology Assessment |
| HTDS | High Tech Drug Scheme |
| IBTS | Irish Blood Transfusion Service |

| | |
|---|---|
| ICER | Incremental Cost Effectiveness Ratio |
| ICORN | Irish HCV Outcomes Research Network |
| IDU | Intravenous Drug Use |
| IPHA | Irish Pharmaceutical Healthcare Association |
| LTI | Long Term Illness scheme |
| MSM | Men who have Sex with Men |
| NCPE | National Centre for Pharmacoeconomics |
| NHANES | National Health and Nutrition Examination Survey |
| NICE | National Institute for Health and Care Excellence |
| NS 3/4A | Non-structural Protein 3/4a |
| NTR | Non-translated region |
| OR | Odds Ratio |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PCR | Polymerase Chain Reaction |
| PCRS | Primary Care Reimbursement Service |
| Peg-IFN | Pegylated Interferon |
| PEG | Pegylated Interferon |
| PI | Protease Inhibitor |
| PSA | Probabilistic Sensitivity Analysis |
| QALY | Quality Adjusted Life Year |
| RBV | Ribavirin |
| RCT | Randomised Controlled Trial |
| RVR | Rapid Virological Response |
| SD | Standard Deviation |
| SF-36 | Short-form 36 |
| SVC | Spontaneous Virological Clearance |
| SVR | Sustained Virological Response |
| SVR 12 | Sustained Virological Response 12 weeks post-treatment |
| SVR 24 | Sustained Virological Response 24 weeks post-treatment |
| TACE | Transarterial Chemoembolisation |
| UK | United Kingdom |
| US | United States of America |
| VAS | Visual Analogue Scale |
| WHO | World Health Organisation |

| | |
|---|---|
| WTP | Willingness to Pay |
| 95% CI | 95% Confidence Interval |

# Chapter 1

# 1 Introduction

Chronic Hepatitis C (HCV) is an important public health concern with an estimated 20,000 to 50,000 people infected in Ireland (1). Of those, only the minority (approximately 12,000) are diagnosed and fewer still (approximately 8,000) have engaged in tertiary level hepatology care (2). At the present time, HCV therapeutics is undergoing enormous expansion with novel agents promising all oral regimens with minimal side-effects and excellent efficacy (3-6).

Between 2004, when HCV became a notifiable illness in Ireland, and 2012, 11,527 cases were notified to the Health Protection Surveillance Centre (7). In 2012, 1036 cases were notified, a decrease of 18% when compared to 2011. The majority (74%) came from the Health Service Executive (HSE) East region. Injecting drug use is the most frequently identified acquisition risk factor (74%) and the majority (82%) of patients were aged between 25 and 54 years (7). World-wide, HCV is a leading cause of morbidity and cancer-related death (8). There are 6 different genotypes of HCV of which genotype 1 and 3 predominate in Ireland (9). The HCV genotype acquired by the patient has implications for the response to and duration of HCV treatment. From 2000-2012 the standard of care treatment was a combination of weekly subcutaneous pegylated interferon with twice daily oral ribavirin (10). With this treatment regimen, patients infected with genotype 1 virus required 48 weeks of therapy and achieved a sustained viral response (SVR) or "cure" in approximately 40% of cases. Those with genotype 3 infection could be treated with 24 weeks of pegylated interferon and ribavirin and achieve an SVR in approximately 80% of cases (10). Low treatment response rates and significant side-effects resulted in a poor uptake of HCV treatment (11). 2011 saw the licensing in the United States of two new agents for the treatment of HCV, telaprevir and boceprevir. These are NS3/4A protease inhibitors with activity against HCV genotype 1 infection. They are licensed for use as add on treatments to a background regimen of pegylated interferon and ribavirin and significantly improve treatment outcomes for patients with HCV genotype 1 infection (12).

Horizon scanning at the National Centre for Pharmacoeconomics in 2011 identified that HCV therapeutics was undergoing significant expansion and was likely to have a high budget impact in the coming decade. HCV treatment with pegylated interferon and ribavirin had never been assessed for its cost effectiveness in the Irish setting and information is scarce with regards to the demographics of the HCV population, the cost of HCV care and the health related quality of life of this population in Ireland. In light of this, it was proposed to undertake a research programme to address the deficits in the knowledge base in this area, with a view to undertaking a cost-utility analysis of HCV treatment in Ireland. That work has formed the basis of this doctoral thesis.

## 1.1 Aims and Objectives

The aim of this thesis is to perform a multi-technology health economic evaluation of the treatment of HCV genotype 1 infection in Ireland.

The objectives are as follows:

- To establish the national demographics of patients with HCV in Ireland who had undertaken treatment for HCV between 2000 and 2012 and to derive estimates of the budget impact of that treatment
- To establish an accurate cost of HCV care in the Irish health care setting
- To establish health-state utilities for Irish patients infected with HCV, stratified by increasing impairment of liver function
- To derive the relative efficacy of boceprevir versus telaprevir using a mixed treatment comparison model
- To develop a cost-utility model to assess the cost utility of HCV treatment in the Irish healthcare setting

## 1.2 Overview of Thesis Chapters 2 to 9

Chapter 2 provides background information on HCV. It includes comprehensive information on the basic virology of HCV, the spectrum of HCV-related clinical disease, the epidemiology of HCV and the treatment options available.

Chapter 3 introduces the main concepts involved in health economic evaluations. It provides a short overview of the types of analysis and the differences between them. It describes the inputs required for cost-utility analysis, the appropriate methods of reporting the results of economic evaluations and the uncertainty around those results. The second part of the chapter summarises the development of pharmacoeconomic analysis in Ireland. It describes the public funding and reimbursement structures for medicines in Ireland. It concludes with a summary of recent developments in the area of prescribing stewardship which have been implemented with a view to improving the quality of prescribing and the sustainability of the Community Drug Schemes.

Chapters 4 to 8 present the original research of this thesis. Chapter 4 presents the study elucidating the national demographics of HCV treatment experienced patients in Ireland and the budget impact of HCV treatment with pegylated interferon and ribavirin.

Chapter 5 presents the results of the cost of illness study undertaken to establish the cost of HCV care in Ireland. Chapter 6 presents the study on the health-state utility of Irish patients with HCV.

Chapter 7 describes the meta-analysis and mixed treatment comparison by which the relative efficacies of boceprevir and telaprevir were established.

Chapter 8 integrates the results of all the studies presented in Chapters 4 to 7. It describes the development of a cost-utility decision model to address the question of the cost effectiveness of HCV treatment in Ireland. It derives the inputs it requires for baseline demographics, costs, QALYs and efficacy from the results of the previous 4 chapters. It presents the results of the

economic evaluation, the uncertainty surrounding those results and discusses the findings in light of current willingness to pay thresholds.

Chapter 9 briefly summarises the main findings of the original research contained in the thesis and draws final conclusions.

## 1.3 Conclusion

The prevalence of HCV makes it an important public health issue. The arrival of new agents which improve the outcomes of therapy for many patients present an opportunity for successful treatment. The costs of these therapies and the budget impact that they represent, ensure that they are of importance from a health economic perspective. The establishment of Irish values for HCV-related costs and consequences will allow the economic evaluation of HCV treatment in Ireland. It will also enable a more robust assessment of future agents. This is important as the drug development pipeline in this health-care area is extremely prolific. The information derived through the development of this project will be of interest to clinicians, health economists and policy makers alike.

# Chapter 2

# 2 Hepatitis C

## 2.1 Hepatitis C - Basic Virology

Hepatitis C virus (HCV) was first identified as the cause of Non-A, Non-B chronic hepatitis in 1989. It belongs to the family flaviviridae and genus Hepacivirus (13, 14). It is an RNA virus that is transmitted person-to-person mainly through blood but also through bodily fluids (15). HCV replicates in hepatocytes where it has a replication rate of $10^{10}$-$10^{12}$ virions per day (16). Host innate immune responses to control acute hepatitis C infection include the expression of interferon-β, interferon regulatory factor 3 target genes and lamba interferons. These act to drive adaptive immunity. Lymphocyte activation is also critically important. CD4+ T-cells and cytotoxic CD8+ T-cells have vital roles in controlling acute infection. Mutations in viral epitopes, targeted by lymphocytes are one method of immune invasion (17). Host factors, such as the presence or absence of various IL-28B alleles or KIR2DS3 genes can also influence the efficiency with which the host is able to control the immune response (18).

The high replication and mutation rate of the virus along with the various methods of immune evasion enable it to establish a chronic infective state. Once chronic infection is established it causes inflammation in the hepatocyte (hepatitis) and eventual cell death. Cell death occurs through both the viral reproduction itself and the host's immune responses against the infected cells. The cycle of viral replication and cell death leads to pronounced scarring of the liver parenchyma, and a clinical state known as cirrhosis.

The exact life cycle of the HCV virus is still a matter of research however the following steps are known to be important:

### 2.1.1 Viral Entry

This is a complex multi-step process that is incompletely understood. (Figure 2-1)

1. The HCV Envelope proteins E1 and E2 attach to receptors on the cell membrane. These receptors come from different cell classes. SCARB1 (scavenger receptor class B type 1) and the tetraspanin CD81 are the best characterised. SCARB1 was first identified as a major receptor for High density lipoproteins (HDL). It has the ability to mediate E2 binding. CD81 appears to prime HCV envelope proteins for a low pH-dependent fusion. CLDN1 and OCLN are transmembrane tight junction proteins that appear essential for viral entry, although their role is unclear. They may act as partners with CD81. Recently, epidermal growth factor receptor (EGFR) and Ephrin receptor A2 (EphA2) have been identified as co-receptors. As the HCV envelope is predominantly made up of cholesteryl esters it has the ability to interact with lipoproteins. Lipoprotein lipase has the ability to modulate HCV entry, although this may result in a non-productive pathway (14, 16).
2. The virus penetrates the cell surface membrane and is then internalised by clathrin-mediated endocytosis. It reaches the cell body by retrograde actin transportation. The exact role of HCV co-receptors in endocytosis remains undetermined (14, 16).

3. The viral envelope fuses with the hepatocyte cell membrane and the nucleo-capsid is released into the cell cytoplasm. There the RNA genome is uncoated (14, 16).

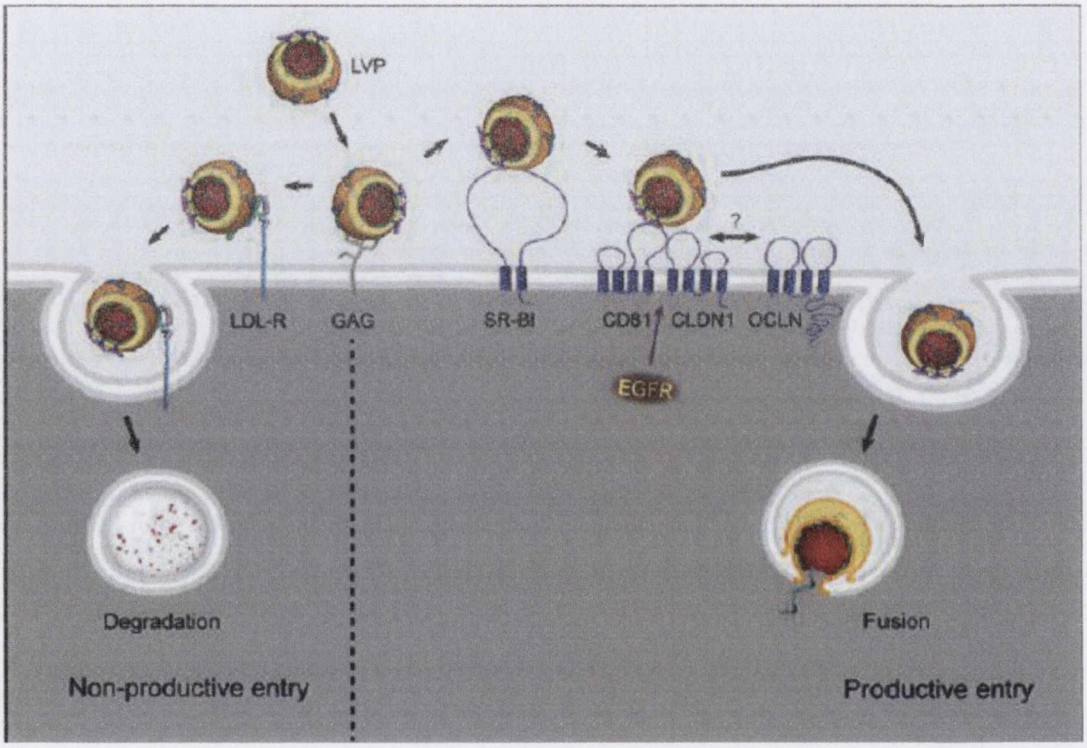



**Figure 2-1 HCV entry to host cell.**
*Ploss and Debuisson (16)*

## 2.1.2 HCV RNA translation and replication

*(Figure 2-2, Steps D and E)*

4. The HCV genome is flanked by two non-translated regions (NTR) at the 5' and 3' regions which are critical for its translation and replication. The 5'NTR contains an internal ribosome entry site, which initiates translation of the polyprotein (14, 16, 19).

5. Following translation, the RNA molecule undergoes post-translation processing. It is cleaved by host and viral proteases into 10 mature structural and non-structural proteins (core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). The structural proteins are two envelope proteins (E1 and E2) and a nucleocapsid core protein that are required for virus assembly along with the p7/NS2 junction. The non-structural proteins include two proteases (NS3, NS4A), a helicase (NS3) and an RNA polymerase (NS5B) required for protein maturation and viral replication (14, 16, 19).
6. The HCV proteins are associated with membranes from the endoplasmic reticulum. NS3 through NS5B act as the replication machinery. This produces positive-sense HCV–RNA molecules from a template of a complementary negative-sense RNA molecule. This replication machinery is located in the "membranous web" or "double membrane vesicle" which is an accumulation of Endoplasmic Reticulin (ER) derived membrane vesicles and lipid droplets induced by NS4B (14, 16).
7. Host factors such as cyclophilin A and phosophatidylinositol 4 kinase IIIα (PI4KIIIα) have a critical role in promoting viral replication through their interaction with NS5A (16).

### 2.1.3 HCV Assembly

*(Figure 2-2, Steps F-G)*

This is the least understood part of the life-cycle and is intricately connected to lipid metabolism.

8. Structural and non-structural proteins interact with the components of lipid metabolism at different stages of the assembly process. Lipid droplets in

infected cells cluster in the peri-nuclear region where they are associated with the core protein. NS2, p7 and the E1E2 heterodimer travel together to the assembly site. NS5A has a central role in the transition from translation to assembly. Once the viral particles are accumulated near the lipid droplets, assembly can start. This consists of nucleocapsid formation, viral budding and maturation. The VLDL assembly pathway is closely related to the infectious particle assembly pathway and ApoB and microsomal transfer protein (MTP) have been associated with particle assembly. Again, the exact mechanisms leading to the lipoviroparticle is poorly understood (14, 16).

9. These virions are then released by exocytosis which provides the budding virion with a further envelope which it uses to attach to the next hepatocyte. This cycle of virion replication continues until the host cell dies. (16)

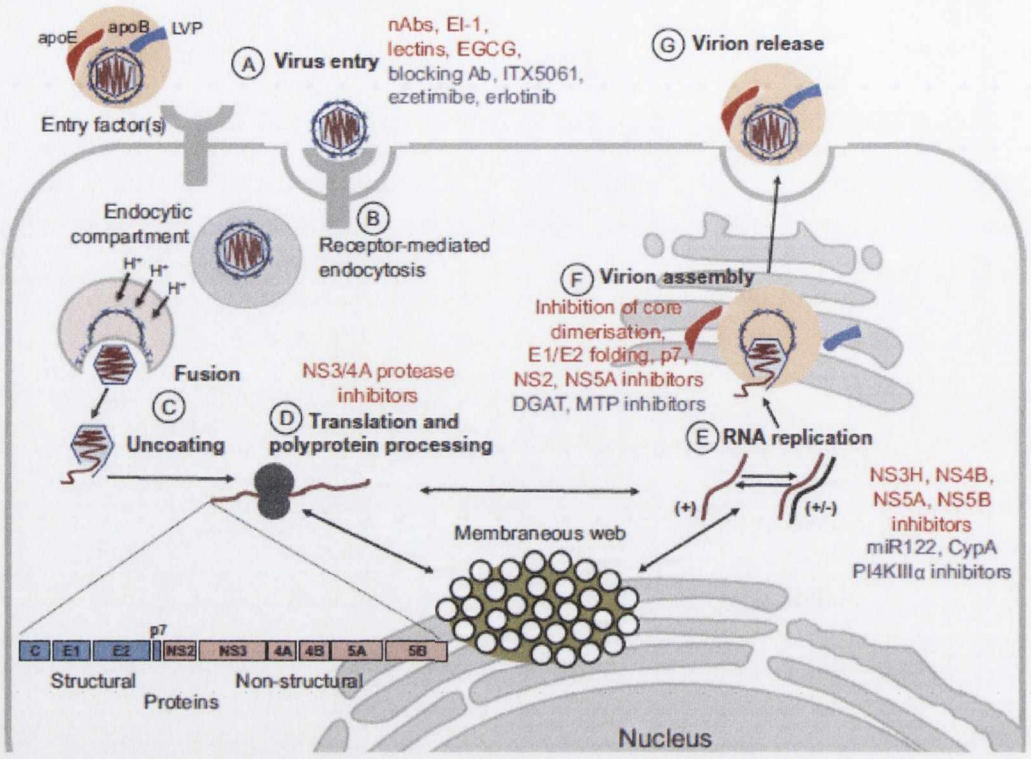



**Figure 2-2 Hepatitis C virus lifecycle.**

*Ploss and Dubuisson (16)*

## 2.2 HCV Genotypes

There are at least 6 HCV genotypes (1-6) with more than 50 subtypes (designated a,b,c etc) These genotypes can vary in their nucleotide sequence by as much as 31-34% with subtypes differing by 20%-23% based on full genomic sequence comparisons (13, 15). Genotype 1 is the most common cause of HCV infection world-wide (8). There is wide geographical variation in the genotypes which predominate in different parts of the world *(Table 1).* In Ireland, Genotype 1 infection is estimated to be responsible for approximately 55% of infections with Genotype 3 accounting for the majority (39%) of remaining infections (1). The HCV genotype has important implications for response to therapy although it does not appear to affect disease progression (20).

**Table 2-1 Global Distribution of HCV genotypes**

| Genotype | Geographical distribution |
|---|---|
| 1a | North and South America, Northern Europe, Australia |
| 1b | Southern and Eastern Europe and Japan |
| 2a | Japan and China |
| 2b | The US and Northern Europe |
| 3a | Australia and South Asia |
| 4 | Middle East, Egypt and central Africa |
| 5 | South Africa |
| 6 | Asia |

### 2.2.1 HCV Transmission Routes

HCV is transmitted very efficiently in blood and bodily fluids. It is estimated that the risk of contracting HCV infection through an occupational percutaneous exposure is approximately 1.8% (range 0%-10%) (15). The majority of infections world-wide are now contracted through intravenous drug-use, however historically there were large numbers of infections from infected blood-products and mass vaccination campaigns. The routes of transmission are summarised below. *(Table 2-2)*

**Table 2-2 Routes of HCV Aquisition**

| Route of Transmission |
|---|
| 1. Blood and Blood Product administration and Organ Transplantation |
| 2. Intravenous drug use |
| 3. Sexual activity |
| 4. Mother-to-Child |
| 5. Parenteral e.g. Tatooing and Acupuncture |
| 6. Iatrogenic Exposure |
| 7. Occupational Exposure |

## 2.3 HCV in the Host

### 2.3.1 Natural History of HCV infection

The course of HCV infection is quite varied. Up to 15% of people infected may clear the virus spontaneously. The remaining 85% are likely to progress to Chronic HCV infection, which is defined as a persistent viraemia six months post-infection (21, 22). The spontaneous clearance of HCV is likely related to host polymorphisms in T-cell function, especially the presence of certain IL-28B alleles in conjunction with genes regulating NK cell expression such as KIR2DS3 (18). The subsequent course of HCV infection is also very individual, with some hosts progressing to end-stage liver disease more swiftly than others. In general, the course of the infection is relatively indolent with approximately 15%-30% of patients developing cirrhosis within 30 years (17, 21-23).

### 2.3.2 Acute HCV infection

The majority of patients with acute HCV are asymptomatic. Approximately 20%-30% will experience symptoms such as abdominal pain, nausea, vomiting and fatigue and have signs such as jaundice and hepatosplenomegaly. Symptoms generally occur within 4-12 weeks and persist for 2-12 weeks. Within 6 weeks of infection, Hepatitis C viraemia is detectable using polymerase chain reaction (PCR) technology. HCV antibodies are generally detectable within 12 weeks (15, 22, 24).

There has been increasing interest in the treatment of acute HCV recently. In a review of patients treated with 24 weeks of pegylated interferon after documented acute HCV, viral clearance occurred in 70%-90%. There was no additional benefit gained from the addition of ribavirin. The optimum results were obtained in patients with persistent viraemia 3 months after infection and before 12 months of infection (24). While this strategy is undoubtedly attractive, there is difficulty in case-finding as the majority of patients are asymptomatic with their acute infection.

For those patients who spontaneously clear HCV, the HCV antibodies will remain positive (indicating exposure), while the PCR becomes negative (indicating viral clearance). At the present time, there is little evidence to suggest that patients who are PCR negative have any adverse clinical outcomes (17). However there is some suggestion from longitudinal state-infected cohorts that the exposure may impact on quality of life (25).

### 2.3.3 Chronic HCV infection

For those patients who develop chronic HCV, the progression of liver disease is unpredictable and very variable. Many patients progress slowly and asymptomatically

over the course of 20-40 years. The end result of persistent viral replication and hepatocyte inflammation is the development of fibrosis. With increasing amounts of fibrosis and regeneration, there is distortion of the liver architecture. This interferes with the normal flow of blood through the liver and therefore its elimination and synthetic functions. This clinical state is known as cirrhosis. Aside from the morbidity of cirrhosis itself, it predisposes to the development of hepatocellular carcinoma (HCC). It is estimated that 20% of patients will develop cirrhosis over the course of 20 years. For those with cirrhosis, 6% will develop decompensated cirrhosis (the presence of ascites, variceal bleeding or hepato-renal syndrome) and 4% will develop HCC (13, 17, 22, 23).

There are a myriad of rare extra-hepatic manifestations of Hepatitis C. These include porphyria cutanea tarda, glomerulonephritis, keratoconjunctiva sicca, cryoglobulinemia, sero-negative arthritis and cognitive impairment. The presence of any of these extra-hepatic manifestations is an indication for HCV treatment, regardless of the stage of liver fibrosis (13, 26).

There are a number of different methods of classifying disease progression in HCV. These methods are based on clinical findings, histological criteria or a non-invasive technique called transient elastography. For many patients their progression to end-stage liver disease is demonstrated by a clinical manifestation of liver failure, such as the development of ascites or by characteristic findings of cirrhosis on liver ultrasound. The classification of HCV-related liver disease on histological grounds requires a liver biopsy. This is usually performed to provide information on whether a patient has mild or moderate liver fibrosis and to out rule co-existing causes of liver disease. Once a patient has clinically or radiologically evident cirrhosis, the risks of

liver biopsy generally outweigh the potential for added diagnostic information. There are a variety of histological grading systems for HCV-related fibrosis in current use. The modified Ishak Score is the one most commonly reported from Irish laboratories. It reports the fibrosis score on a scale of 0-6 and also gives a report on the activity level seen. An Ishak score of 0-2 would be considered mild fibrosis, a score of 3 or 4 would indicate moderate fibrosis and a score of 5 or 6 would be suggestive of cirrhosis (27). The other commonly used histological grading system for HCV related fibrosis is the Metavir staging system. This categorises liver fibrosis into 4 stages F1-F4. F0/1/2 are generally considered mild, F3 is suggestive of moderate fibrosis, while F4 suggests cirrhosis (28, 29). Recently, non-invasive tests of liver "stiffness" have become more available in clinical practice. Transient elastography allows estimation of the degree of liver fibrosis without the need for a liver biopsy. It has good discriminatory performance in assessing no fibrosis from cirrhosis but has poorer discriminatory function in differentiating between mild and moderate degrees of fibrosis (30, 31). Table 2.3 compares the clinical, histological and transient elastography staging systems for degrees of liver fibrosis.

**Table 2-3 Comparison of clinical, histological and transient elastography (TE) scoring systems**

| Clinical Stage | Modified Ishak Score | Metavir Score | TE cut-off values in HCV |
|---|---|---|---|
| Mild | 0, 1, 2 | 0, 1, 2 | < 8.8 |
| Moderate | 3, 4 | 3 | > 8.8 < 14.6 |
| Cirrhosis | 5, 6 | 4 | > 14.6 |

### 2.3.4 End Stage Liver Disease

*Cirrhosis*

The majority of patients with Hepatitis C are asymptomatic. As end-stage liver disease develops, symptoms start to emerge. Most patients report increasing fatigue, muscle weakness, itch and GI upset. On clinical examination, jaundice, ecchymoses, spider naevi and muscle wasting may be apparent. With increasing impairment of liver function, liver decompensation may occur. Fluid may accumulate in the peritoneal cavity, a condition known as ascites. Oedema of the gastrointestinal mucosa can lead to translocation of gut bacteria across the luminal wall and the development of spontaneous bacterial peritonitis. Increased portal venous pressure can lead to dilation of the submuscosal vessels in the stomach and oesophagus. These can rupture, giving rise to catastrophic upper gastrointestinal haemorrhage. Also as a result of increased portal pressure the spleen may enlarge with resultant hypersplenism. The accumulation of toxic metabolites, frequently in the presence of a super-imposed infection or bleed, can lead to deterioration in cognitive function. This is known as hepatic encephalopathy. Renal impairment may occur in the setting of profound liver impairment, a condition known as hepatorenal syndrome (32).

For patients who develop decompensated cirrhosis, the only definitive treatment is liver transplantation. HCV-related liver disease is the leading cause of liver transplantation world-wide and was responsible for 44% of liver transplantation procedures in Ireland between 2000-2013 (33). HCV re-infection of the graft is universal and the course of the disease is accelerated. The majority of patients progress to cirrhosis within 5 years. It is therefore recommended that patients be treated for HCV prior to transplantation or once chronic infection is established in the transplanted organ (34-36).

*Hepatocellular Carcinoma (HCC)*

HCC develops in patients with severe cirrhosis. It is the 5$^{th}$ most common malignancy in men and the 2nd most common cause of cancer death world-wide (37). The WHO estimates that there were 782,000 incident cases and over 745,000 deaths worldwide in 2012 (37). Thus the prognosis is very poor. Many patients present late, leaving treatment options limited. Radio-frequency ablation and partial resection are possible with smaller tumours, although recurrence is common. Sorafenib is a multi-kinase inhibitor which has been used to defer disease progression. The only curative option is liver transplantation but only a minority of candidates are suitable for this strategy (38).

Recent observations indicate that the incidence of HCC is the third fastest growing amongst all cancers. In the United States (US), there has been an 80% increase in the incidence of HCC in the last 20 years (37, 38). In the United Kingdom (UK), liver cancer incidence is the second fastest growing in males and the fourth fastest in females (39). HCV is an important risk factor for HCC. Patients with chronic HCV are 15-20 times

more likely to develop HCC (38). HCV positivity has been reported in 80%-90% of HCC patients from Japan, 44%-66% of HCC patients in Italy and 30% to 50% of patients with HCC in the US (38).

In Ireland, rates of HCC have been increasing. In 1994, the age standardised incidence rate for hepatocellular carcinoma was 1.9 per 100,000. In 2009, this had increased to 3.4 per 100,000, an increase of 79%. For patients diagnosed with HCC in Ireland between 1994 and 2004 the 1-year survival rate was 47% with a 5-year survival rate of 24% (40). HCC has been the indication for liver transplantation in 10% of patients (n=60) undergoing transplant in Ireland over the last 10 years. Of those receiving a transplant for this cause, HCV is the most common underlying diagnosis (n=15, 25%) (33).

### 2.3.5 Risk Factors for progression to End-Stage Liver Disease with HCV

While the progression to end stage liver disease is difficult to predict, a number of risk factors for more rapid progression have been identified. These include male gender, heavy alcohol consumption, co-infection with HIV and older age (17, 21).

*Alcohol consumption*

There is strong evidence that alcohol consumption in excess of 50g per day has an important effect on the progression of fibrosis in HCV. Excessive alcohol intake has been shown to increase the progression to cirrhosis three-fold. Moderate alcohol (>20g/day) has been shown to be a significant factor in the progression of mild to moderate cirrhosis. It is unclear as to whether HCV and chronic alcohol abuse are independent risk factors or additive in their effects (17, 20, 41).

*Older age*

Older age at acquisition of HCV infection is an important predictor of time to progression of fibrosis. Patients who were infected over the age 50 years showed more rapid progression of liver disease than those infected at an earlier age. There also appears to be a correlation with increasing age and poorer response to treatment (20, 34).

*Male gender*

Male gender has been associated with higher rates of decompensated cirrhosis, liver transplantation and death in HCV patients (20, 41).

*Co-morbidities and Co-infections*

Co-infection with HCV occurs frequently in HIV-infected intravenous drug users (IDU) (42), those who acquired Human Immunodeficiency Virus (HIV) infection through contaminated blood products (43), and increasingly in HIV-infected men who have sex with men (MSM) (44, 45). HIV modulates the clinical course of HCV. It has been shown to decrease spontaneous clearance of HCV, accelerate progression to end-stage liver disease and to reduce response to interferon therapy (46, 47). Since the advent of highly active anti-retroviral therapy the incidence of and mortality from Autoimmune Deficiency Syndrome (AIDS) related illnesses in HIV infected patients has fallen dramatically (48, 49). Recent large cohort studies have reported HCV-related liver disease as a leading cause of morbidity and mortality in HIV/HCV co-infected patients (49-52).

Hepatitis B co-infection with Hepatitis C also increases the rate of development of severe fibrosis (47). Diabetes mellitus has been implicated in disease progression. It has been shown to be a risk factor for the development of HCC in HCV infected patients (17, 53).

*Duration of infection*

A number of meta-analyses looking at rates of progression of liver disease in HCV have identified the duration of HCV infection as the most robust indicator of fibrosis progression (20, 41). Duration of infection was found to be an independent predictor at all stages of liver fibrosis. The progression of fibrosis is likely to be non-linear. For the first 10 years of infection fibrosis progression is approximately linear with an exponential increase subsequent to this (41). (*Figure 2-3)*

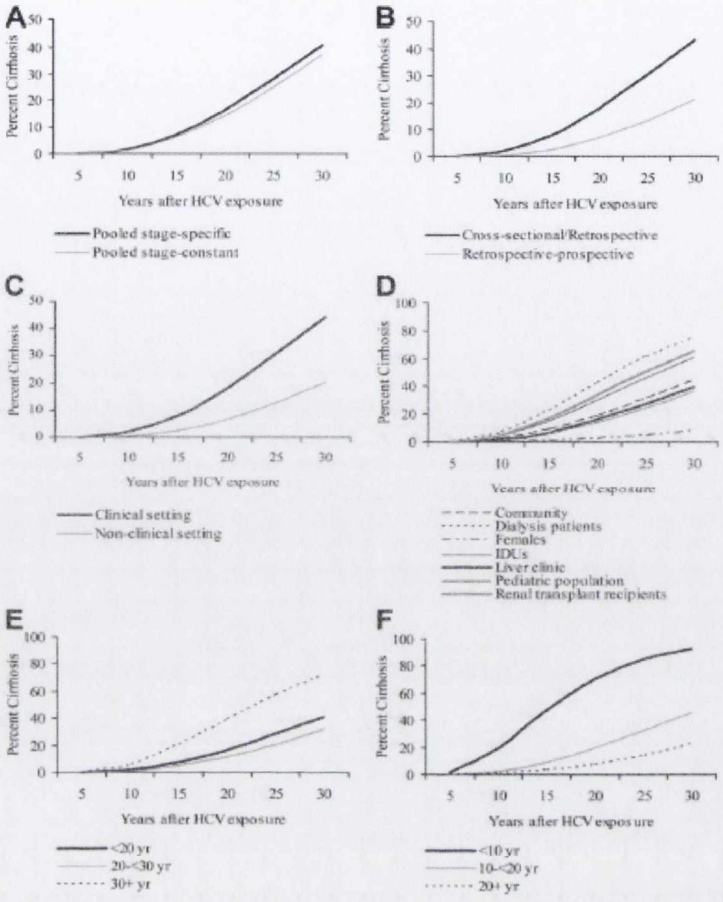



Fig. 2. Comparison of predicted cumulative rates of cirrhosis by: (A) transition probability estimation method; (B) study design; (C) setting; (D) selected study population; (E) age at HCV infection; and (F) duration of HCV infection. HCV, hepatitis C virus; IDUs, injecting/intravenous drug users. Note: Projections are based on unadjusted transition probabilities and may be confounded by the effects of other covariates; for example, study design.

**Figure 2-3 Progression of liver fibrosis with duration of HCV infection**
*Thein et al.* (41)

## 2.4 Epidemiology of Hepatitis C

### 2.4.1 Prevalence of HCV in Europe

HCV is a world-wide public health problem. The WHO estimates that 185 million people are chronically infected world-wide with HCV. Every year, 3-4 million people are infected with HCV and 350,000 die from HCV-related liver disease. The estimated prevalence of HCV is highest in Central and East Asia (3.8% and 2%) and in the North Africa/Middle East regions (3.6%) (8). In Europe there are high rates of HCV positivity especially in southern European countries. There are varying prevalence rates across countries in the EU with Italy being estimated to have a population prevalence of 6-8% and the UK <1% (54). *(Figure 2-4)*

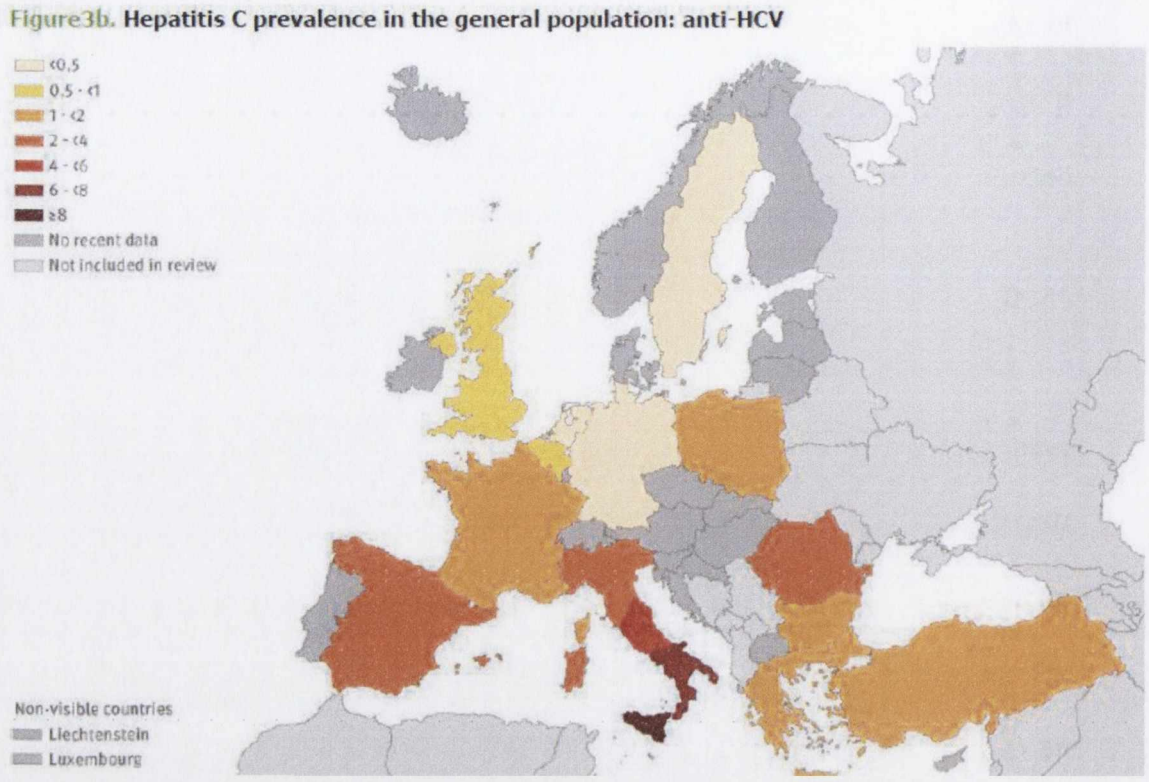



**Figure 2-4 Prevalence of HCV in Europe 2009**
*ECDC (54)*

## 2.4.2 Prevalence of HCV in Ireland

The prevalence of HCV in Ireland is poorly characterised. It is likely that the majority of infected patients remain undiagnosed. A publication linking notifications to virology laboratory results in Ireland estimated that there are between 30,000-50,000 patients with chronic HCV in Ireland (1). Other than this, there have been small prevalence studies in high-risk populations in Ireland. A number of studies of HCV antibody prevalence in IDUs in prisons, opiate substitution services and general practice in Ireland, between 1992 and 2006, estimated it to be between 52% and 84% in this population (55-62). In 2011, a cross-sectional study reported lower levels of HCV

antibody positivity in the prison population, with 41.5% of those with a history of IDU, and 54% of those with a history of injecting heroin, testing positive for anti-HCV (63).

A study of voluntary infectious disease screening of asylum seekers attending the Balseskin reception centre, between 2004 and 2012, found that 1% of those tested were positive for chronic HCV infection (64).

Available data on populations outside the known high-risk groups indicate that the HCV prevalence in the general population in Ireland is likely to be low. Two recent studies of universal hepatitis C screening in large Dublin maternity hospitals found anti-HCV antibody prevalences of 0.7 and 0.9% in their antenatal populations (65, 66). Irish Blood Transfusion Service (IBTS) blood donor screening between 1997 and 2013 found that 0.02% of first time blood donors were anti-HCV positive (67).

### 2.4.3 Prevalence by Route of transmission

*Unsafe Medical Practices*

Historically, the prevalence of HCV infection was related to the prevalence of infected blood and blood-products and to unsterile health-care associated injecting practices. Prior to 1992, 90% of HCV infections in the US were related to post-transfusion infection with 2% -10% of blood units in developed countries transmitting HCV (8, 68). This has been dramatically reduced through measures which include the screening of all blood donors for anti-HCV antibodies and effective methods of virus-inactivation for blood units. No blood/blood product related infection have been reported in Europe since 1994 (68). The majority of infections acquired by this route are Genotype 1 infections (68). There are large legacy issues surrounding these infections in Ireland and other countries. In 2004 in Ireland, the National HCV database was set

up as a longitudinal study of liver-related outcomes in patients who were state-infected with HCV. This provides a valuable resource for the natural history and treatment outcomes in an Irish cohort of patients (69). Unsterile health-care associated injecting practices related to mass vaccination programmes in the 1950s and 1960s are responsible for the majority of HCV cases in Southern Europe (68). The epidemics in these countries are driven by these historical exposures. These cohorts are now aging and in Italy and France it is possible that the peak of the epidemic has been reached with prevalence now declining (70).

*Intravenous Drug Use*

In Ireland and other northern and eastern European countries the majority of patients infected with HCV acquired their blood-borne virus infection through repeated unsterile percutaneous exposure in the setting of illicit intravenous drug use (IDU) (68). Patients acquiring HCV in this way are younger and are responsible for the majority of incident cases at the present time. As many are unaware of their diagnosis, they continue to fuel the epidemic of HCV.

Genotype 1a and Genotype 3a infection are associated with IDU while genotype 1b and 2 are associated with unsafe medical practices (68). In Ireland it is estimated that up to 70% of Dublin intravenous drug users are infected with HCV (57). As this population ages, it is likely that there will be increasing levels of liver-related morbidity and mortality related to HCV.

### 2.4.4 Incidence of HCV

In 2009 there were 27,354 incident cases of HCV reported from 26 EU countries. This gives an incidence rate of 8.19 per 100,000. In Ireland in 2012, 1036 cases were

reported, a decrease of 18% compared to 2011. The majority were male (66%), were aged between 25-54 years (82%). Intravenous drug use was the most frequently reported mode of acquisition (74%) (69). The numbers of reported incident cases have continued to fall *(Figure 2-5)*. A recent study was carried out using Health Research Board National Drug Treatment Reporting System data with a view to estimating the likely duration of HCV infection in IDUs in Ireland. All injecting drug users entering treatment between 1991 and 2010 were identified and the year they commenced injecting was determined. The incidence of HCV infection and chronic HCV infection were then estimated by applying published infection and chronicity rates to this population. This suggests that the peak of the incident HCV epidemic in IDU in Ireland is likely to have occurred in the mid-nineties and many of these patients will now have been infected for greater than 20 years (71).

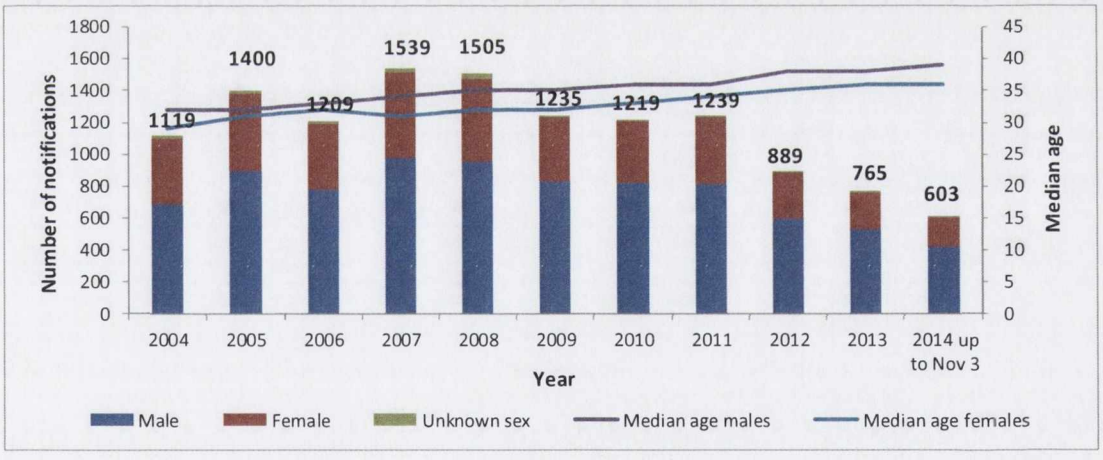



**Figure 2-5 Incidence of HCV in Ireland 2004-Nov 2014**
*Reproduced with permission from Dr. Niamh Murphy, HPSC* (72)

### 2.4.5 Impact of Aging

The population infected with HCV is aging in the US and other countries. Results from the fourth National Health and Nutrition Examination Survey (NHANES IIII) showed that the majority of people infected with HCV in US were now in the 40-49 year age

bracket. This contrasts with the results from NHANES III conducted 5 years prior to this, when the majority of infected patients were in the 30-49 year age bracket (73). *(Figure 2-6)*

*Figure 2.* **Prevalence of antibodies to hepatitis C virus (*HCV*) by age group (*A*) and year of birth (*B*) in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) and the current NHANES (1999–2002).**

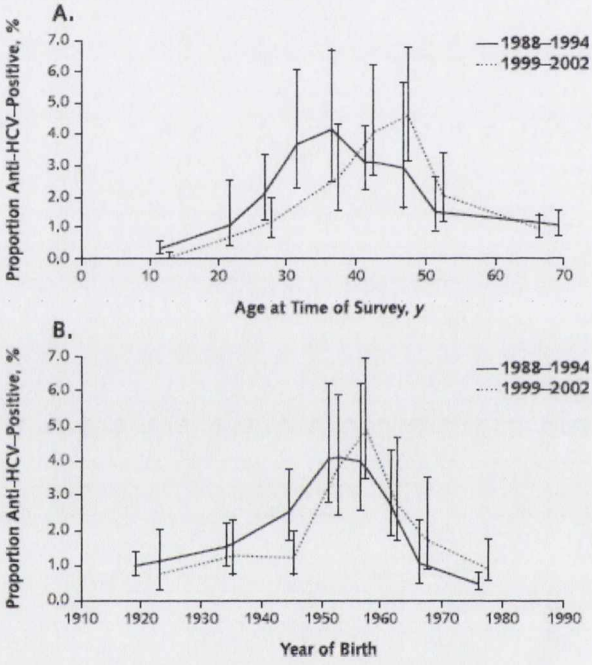



**Figure 2-6 Prevalence of HCV by age group and year of birth in the NHANES study**
*Armstrong et al.* (73)

As the population with HCV ages, the proportion of people with durations of infection greater than 20 or 30 years will increase. The combination of age greater than 50 and prolonged duration of infection is a risk factor for more rapidly progressive liver disease. Therefore, it is likely that an increase will be seen in the incidence of severe manifestations of HCV infection (20, 41). *(Figure 2-7)*

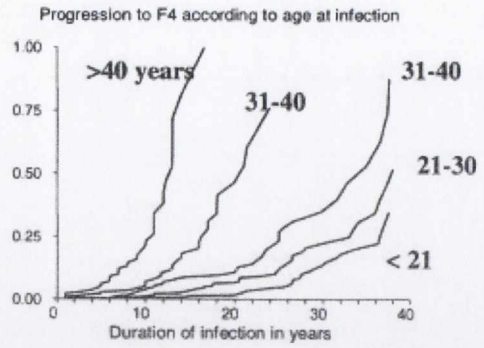



**Figure 2-7 Progression to End-Stage liver disease (Metavir stage F4) depending on age at first infection**
*Thein* et al. (41)

### 2.4.6 Impact on Life-expectancy/morbidity/mortality

Chronic Hepatitis C infection has an impact on liver-related and non-liver related mortality. In a recent study, all-cause mortality in HCV infected patients was 2.35 times higher than HCV-negative controls. Liver-related mortality was 26 times higher and non-liver related mortality was also higher at 1.79 times greater than controls (74). The Centre for Disease Control (CDC) estimates that there are 12,000 deaths from HCV in the US per year. HCV infection is estimated to reduce life expectancy by 8-12 years which is similar to the decrement in life expectancy seen with smoking (74). HCV-related liver mortality has now outstripped HIV-related mortality in HIV/HCV co-infected patients and is seen as the major risk factor for death in patients whose HIV is controlled with effective anti-retroviral therapy (49, 52).

### 2.4.7 Burden of Illness

*Death from HCV*

In the US, deaths resulting from HCV now outstrip those from HIV (75). With prolonged infection, the development of liver fibrosis and subsequent cirrhosis and HCC is more likely (41). As the proportion of patients with HCV for longer than 20

years increases in Ireland, it is likely that we will see an increasing burden on public health resources from the sequelae of end-stage liver disease (20, 41).

### *Acute Medical Admissions in Ireland for HCV-related disease*

Data from the Hospital Information Patient Enquiry system beween 2005 and 2012 reveals over 4000 patients where HCV was listed on their discharge information as the primary reason for admission (72). *(Figure 2-8)*

A further 1800 admissions were coded as other and unspecified cirrhosis of the liver. This discharge code specifically excludes liver admissions related alcohol, toxic and congenital causes. Thirteen percent of these admissions in 2011 and 2012 had HCV listed as a co-diagnosis (72).

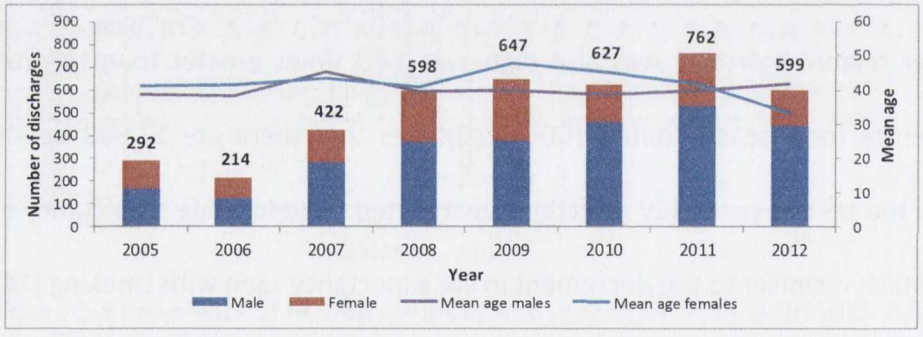



**Figure 2-8 Hospital discharges with HCV as a primary diagnosis in Ireland 2005-2012**
Reproduced with kind permission from Dr. Niamh Murphy, HPSC (72)

### *Hepatocellular Carcinoma*

The rates of HCC in HCV positive patients are 17 fold higher than in patients who are HCV negative (38). Globally, HCC is the 5th most common cancer world-wide with almost 600,000 incident cases (37). In the UK, there has been significant upward trends in HCC incidence and mortality in recent years (39). While the incidence of HCC in Ireland remains low, it has nearly doubled over the last 15 years (76). There is a high mortality from this condition in Ireland with only 24% of patients still alive at 5 years

post-diagnosis (40). *(Figure 2-9)* While HCC notifications are not automatically linked to HCV notifications, between 2010 and 2013, 41% of deaths from HCC had HCV listed as an additional diagnosis. In addition to death, these patients frequently required hospital admissions. There were 1747 hospital discharges with a principal diagnosis of liver cell carcinoma between 2005 and 2012. Fifteen percent of these had HCV listed as a co-diagnosis (72).

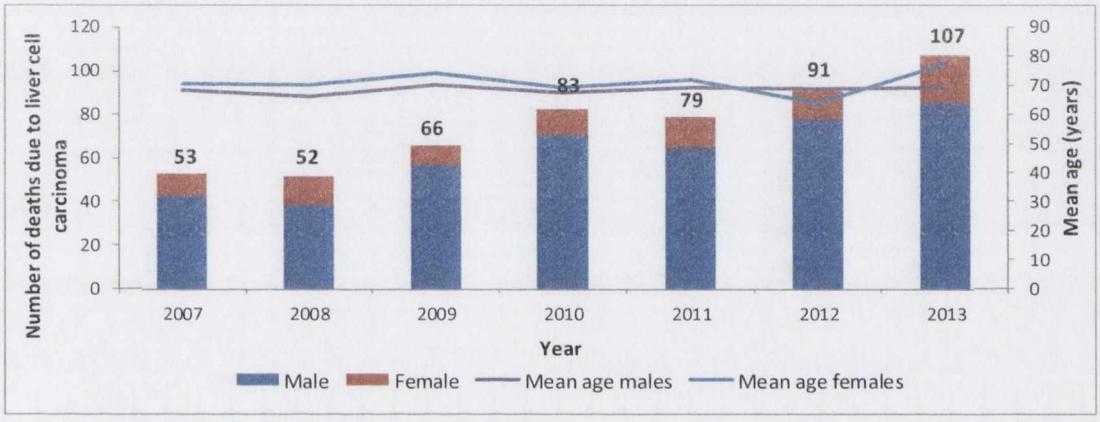



**Figure 2-9 Deaths from HCC in Ireland 2007 – 2013**
*Reproduced with permission from Dr. Niamh Murphy, HPSC* (72)

### *Liver Transplantation*

There has been a continuous rise in deaths due to end-stage liver disease and HCC related to HCV infection in the UK. Concomitant with this, is an increase in the number of patients with cirrhosis secondary to HCV joining the transplant list and the number of transplants performed for HCC (77). In Ireland, underlying HCV is the most commonly listed causative factor of end-stage liver disease in patients undergoing liver transplant beween 2000 and 2013, present in 41% (72). *(Figure 2-10)*

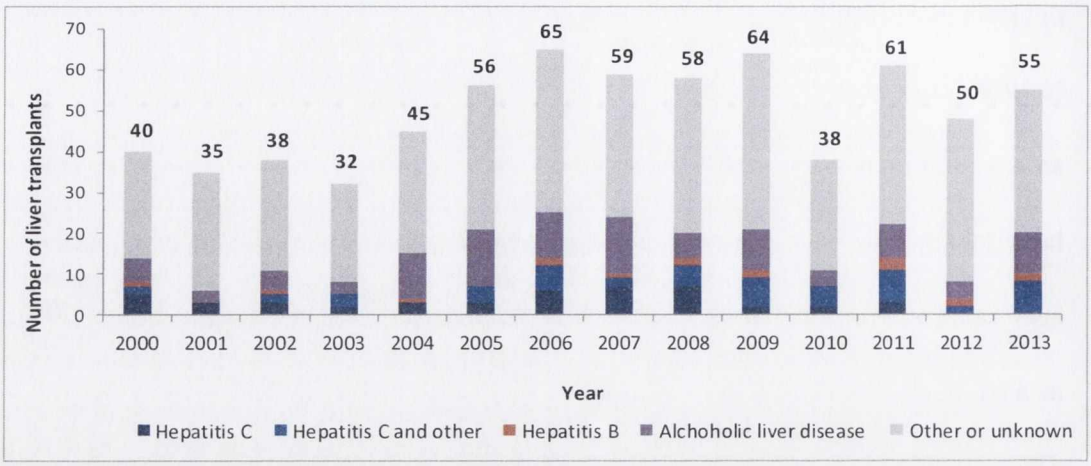



**Figure 2-10 Number of liver transplantations and associated underlying aetiologies 2000-2013**

*Reproduced with permission from Dr. Niamh Murphy, HPSC* (72)

Liver transplantation for HCC is responsible for 10% of transplants under-taken in that time period. In these cases also, HCV is the most common underlying diagnosis (33). As we have a relatively young population with HCV (7), it is likely that the numbers requiring transplantation will continue to rise into the future. This is particularly alarming when you consider that it is estimated that 20,000-50,000 people in Ireland may be infected with HCV (1). In Europe in the last decade, it has been shown that the demand for transplant has increased exponentially while the organs available has remained fairly static. This would bring into question our ability to facilitate increasing numbers of HCV infected patients with this form of treatment (78). (*Figure 2-11)*

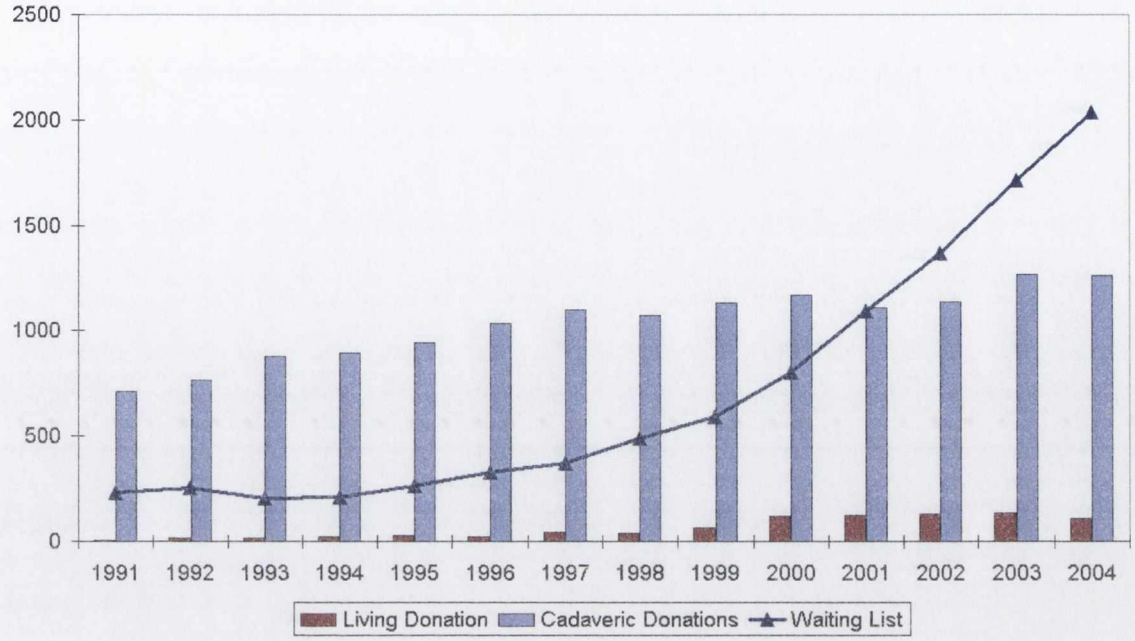



**Figure 2-11 European rates of liver transplantation 1991-2004**
*Muhlberger et al.* (78)

A modelling study performed in France projecting future disease burden and mortality in HCV infected patients predicted that the administration of effective anti-viral therapy would save 14,400 (CI 13,900-15,000) lives (79). In a separate paper the authors projected that the public health burden of HCV in France, now outstrips that of HIV (80).

## 2.5 Treatment of Hepatitis C

### 2.5.1 Standard of Care 2000-2012

From 2000 to 2012, dual therapy with pegylated-interferon (Peg-IFN) and ribavirin (RBV) given for 48 weeks was regarded as the standard of care for treating HCV genotype 1 infection. (12, 81). This resulted in successful treatment outcomes, known as a sustained viral response (SVR) or absence of detectable HCV RNA 6 months post-treatment, in 40-50% of those with genotype 1 infection that were treated (10, 82,

83). For patients with HCV genotypes 2 or 3, 24 weeks of weekly pegylated-interferon with daily ribavirin was generally recommended. This resulted in SVR rates approaching 80% (81).

Treatment with Peg-IFN and RBV results in significant side-effects. Peg-IFN is associated with fatigue, flu-like symptoms, haematological abnormalities and psychological morbidity among a myriad of other side-effects. Ribavirin commonly causes anaemia and is also associated with rash. These side-effects, coupled with the prolonged duration of treatment, commonly affect adherence. This in turn effects efficacy of the treatment (17). Despite the availability of efficacious treatment, uptake of HCV therapy has been limited *(Chapter 4)*.

### 2.5.2 Barriers to treatment

There is extensive literature identifying barriers to HCV care. Key points identified relate to socio-political, individual, and provider-based factors (84). Duration of treatment, low chance of treatment success and fear of adverse effects have all been described as important patient-related barriers to accessing HCV treatment (11, 84). Uncoupling of counselling and testing services from provision of HCV treatment has been identified as a major factor in limiting access to treatment (85). Ongoing IDU and a younger age are patient-related barriers to HCV treatment (11, 84-89).

Provider experience in caring for IDU has been shown to be an important predictor of provider prescription of HIV treatment to this population and this is likely to be true for HCV treatment also (90).

With the advent of more efficacious HCV treatments of shorter durations and minimal side-effects many of the pervious barriers to care will be overcome. Given the cost and

budget impact of these agents, financial constraints are likely to become the pre-eminent barrier to accessing HCV treatment.

### 2.5.3 On treatment: Monitoring Virological Response

During dual therapy with pegylated interferon and ribavirin, the HCV viral load is monitored closely to assess response to treatment. The presence or absence of viraemia at week 4 and week 12 of treatment provides important prognostic information that is used to guide individualised treatment regimens. There are a number of important definitions:

- **Rapid Virological Response (RVR):** HCV PCR is negative at week 4 of therapy.
- **Early Virological Response (EVR):** HCV PCR is negative at week 12 of therapy.
- **Null-response:** < 2 log drop HCV viral load by Week 12. This is an indication to cease therapy.
- **Partial Response:** > 2 log drop in HCV viral load at 12 weeks but still HCV PCR positive at week 24. This is an indication for stopping dual treatment. Partial response may also encompass those patients who become undetectable at some point in therapy but subsequently are PCR + prior to the end of treatment. These patients are also sometimes defined as "**viral rebounders**"
- **End-of-Treatment response (EOTR)**: HCV PCR negative at the end of treatment
- **Sustained Viral Response (SVR24):** HCV PCR negative at 6 months post-treatment. This is essentially considered a clinical cure of HCV
- **Sustained Viral Response (SVR12):** HCV PCR negative at 3 months post-treatment. This is essentially considered a clinical cure of HCV

- **Relapse:** HCV PCR negative at end of treatment but HCV PCR + after ceasing anti-viral therapy.

Treatment-experienced patients are categorised with regards to their on-treatment and post-treatment response to Pegylated interferon and ribavirin *(Figure 2-12)*. Prior treatment response is the most powerful indicator of future treatment response to re-treatment with Peg-IFN and RBV and is likely to remain important with response to Protease Inhibitor-based (PI) therapy (91). Early indications from interferon-free regimens suggest that null-responders remain a more challenging group to treat with some regimens, requiring a longer duration of treatment (92, 93).

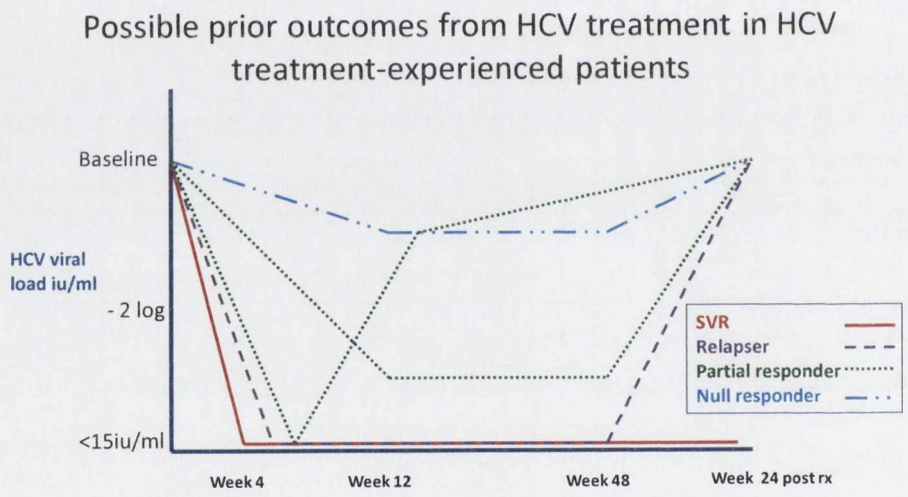



**Figure 2-12 Possible prior treatment response categories**

## 2.6 New HCV Agents

### 2.6.1 NS3/4A HCV Protease Inhibitors

In 2011, the European Medicine Agency (EMEA) licensed two new agents for the treatment of HCV Genotype 1 infection. These were boceprevir and telaprevir. Boceprevir is a non-structural 3(NS 3) serine protease inhibitor of HCV while telaprevir is a non-structural 3/4a (NS3/4A) serine protease inhibitor of HCV. These treatments are used as triple therapy in combination with a backbone of pegylated interferon and ribavirin. Randomised controlled trials (RCTs) of these agents confirm that they have significantly improved efficacy over prior standard of care. Rates of SVR in both treatment naive (94, 95) and treatment experienced patients (96, 97) are dramatically improved and a porportion of patients are eligible for a shorter course of therapy (98). Given their success, there was immense interest from physician and patient groups alike in obtaining access to these medications (17).

They come with additional costs and adverse effects. Both have significantly increased rates of anaemia compared with standard of care. Up to 50% of patients in the RCTs of boceprevir reported anaemia (94). Telaprevir therapy results in the frequent occurence of rash, which may rarely progress to toxic epidermal necrolysis (17).

*First Generation PI-Treatment Regimens and Stopping Rules*

*Boceprevir*

Triple therapy with boceprevir (BOC) commences with a 4 week lead-in of Peg-IFN and RBV. Boceprevir is then added to the treatment regimen. The duration of boceprevir, Peg-IFN and RBV triple therapy is based on the patient's prior treatment history, their underlying liver fibrosis and their on-treatment virological response. Figure 2-13 to

Figure 2-16 summarise the treatment paradigms and stopping rules associated with the use of these regimens in different patient populations.

*Telaprevir*

All patients receiving treatment with telaprevir (TEL), Peg-IFN and RBV commence the three drugs simultaneously and receive a 12 week course of telaprevir. The duration of subsequent Peg-IFN and RBV is dependent on the patient's prior treatment history, their underlying liver fibrosis and their on-treatment virological response. Figure 2-13 to Figure 2-16 summarise the treatment paradigms and stopping rules associated with the use of these regimens in different patient populations.

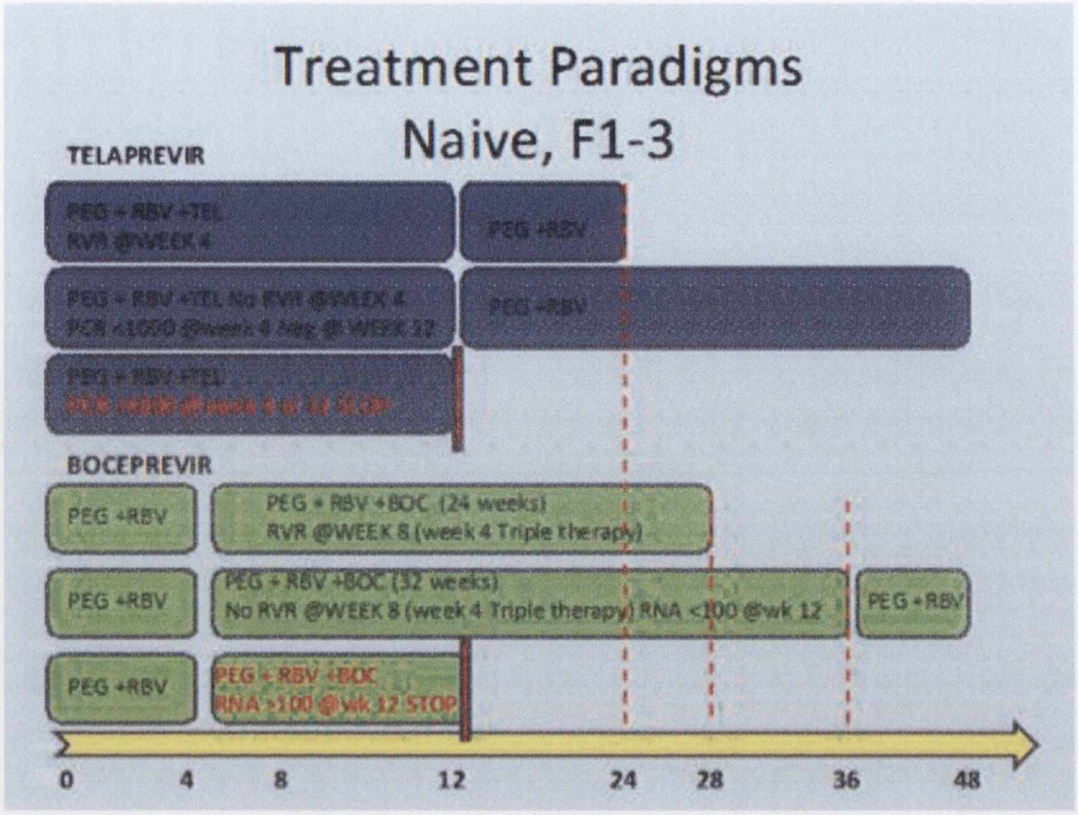



**Figure 2-13 Treatment paradigms for triple therapy with telaprevir and boceprevir in treatment-naive, non-cirrhotic patients**

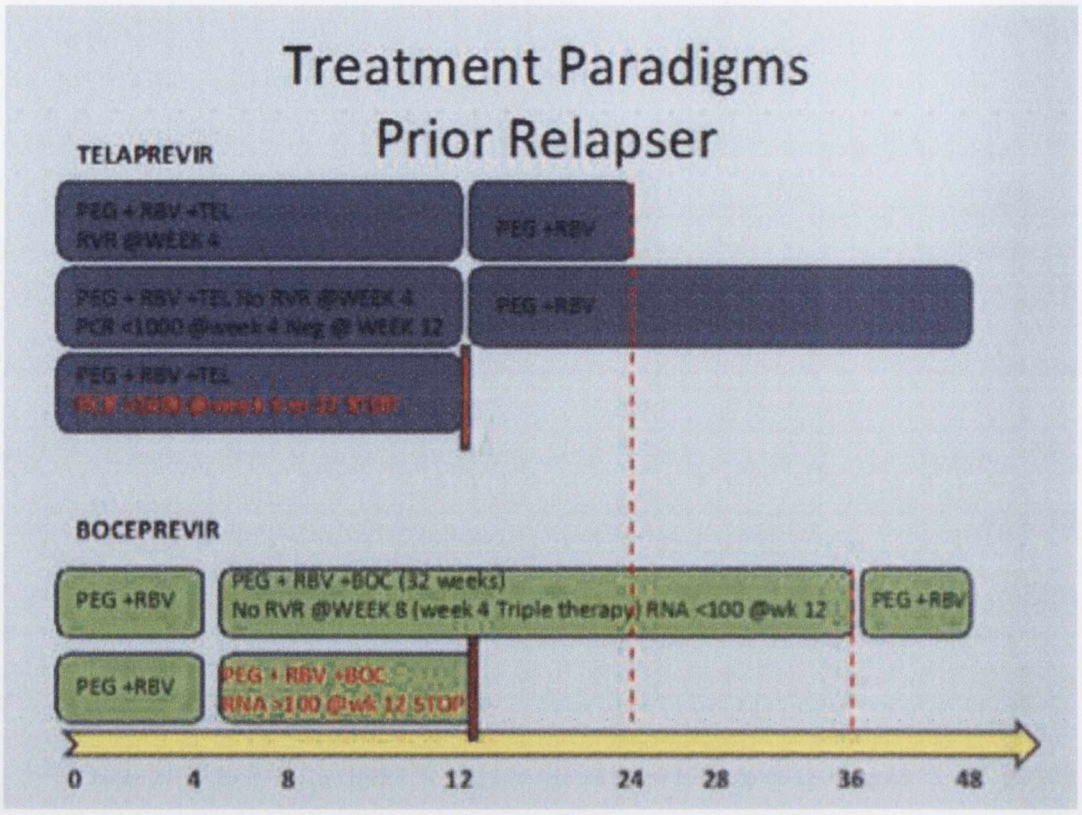



**Figure 2-14 Treatment paradigms for triple therapy with telaprevir and boceprevir in non-cirrhotic patients with a history of relapse post Peg-IFN and RBV treatment**

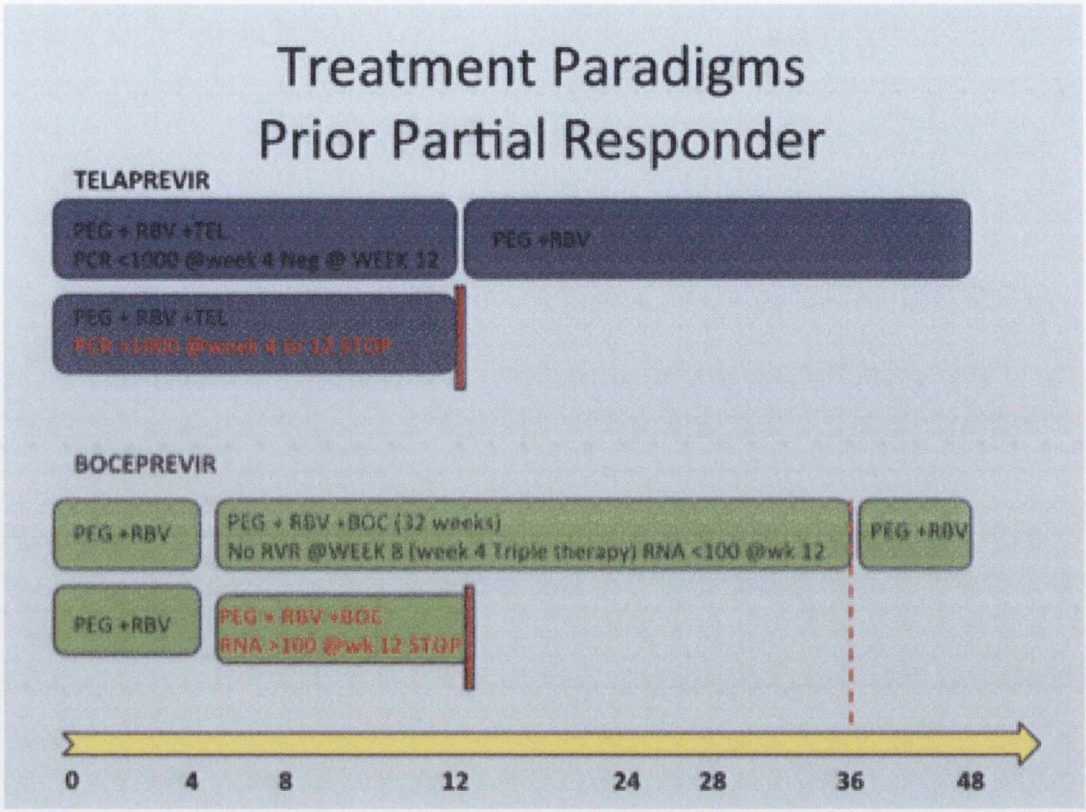



**Figure 2-15 Treatment paradigms for triple therapy with telaprevir and boceprevir in non-cirrhotic patients with a history of partial response to Peg-IFN and RBV treatment**

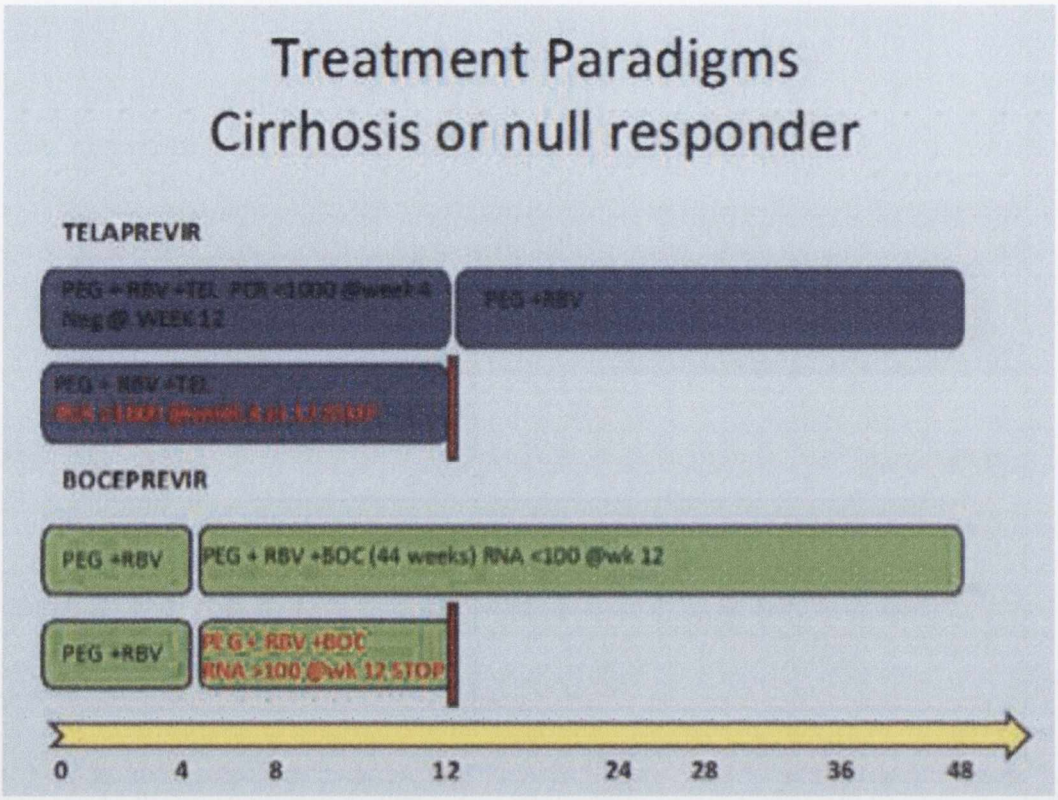



**Figure 2-16 Treatment paradigms for triple therapy with telaprevir and boceprevir for patients with cirrhosis or a history of null response to Peg-IFN and RBV treatment**

### 2.6.2 Pharmacoeconomic Evaluation of 1st Generation HCV PIs in Ireland

Both agents were assessed as single technology assessments by the National Centre for Pharmacoeconomics in Ireland in 2011 and found to be cost-effective (99, 100). This is in accordance with other Health Technology Assessment Agencies world-wide, although the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia found them not to be cost-effective and has not approved them (101, 102). The focus of this PhD will be to examine the cost-effectiveness of HCV treatment in Ireland, considering the treatment options of (1) No treatment, (2) dual therapy with Peg-IFN and RBV and triple therapy with (3) boceprevir or (4) telaprevir in addition to Peg-IFN and RBV.

### 2.6.3 Future Directions in HCV treatment

In 2014, the first of the second generation direct-acting anti-virals (DAAs) was licensed for clinical use. Sofosbuvir is a nucleotide inhibitor which acts on the HCV RNA polymerase enzyme. It is a uridine analogue which inserts into the replicating HCV RNA, causing chain termination. It has broad pan-genotypic activity and a high genetic barrier to resistance. In combination with ribavirin, it offered the first interferon-free regimen for patients with HCV. However, efficacy with this regimen was poor in some genotypes and its licensing limited its use in Genotype 1 patients to those unable to tolerate interferon (103).

It's licensing has been followed by that of simeprevir, a second generation protease inhibitor with improved efficacy and reduced side-effects when compared with the first generation PIs. In combination with sofosbuvir it offers an efficacious, all-oral, interferon-free treatment option for HCV Genotype 1 (103).

In this rapidly evolving field of therapeutics, treatment regimens are developing every 6 months. Ledipasvir, an NS5A replication complex inhibitor was licensed in Europe in Quarter 3 of 2014. This has been co-formulated with sofosbuvir to give a single tablet, all-oral, interferon-free treatment with excellent efficacy and broad genotypic activity. There are other novel agents in advanced Phase 3 development that are expecting licensing in early 2015 (93, 103). Figure 2-17 displays the HCV polyprotein and the sites of action of the novel HCV anti-virals that have been licensed or are in advanced development.

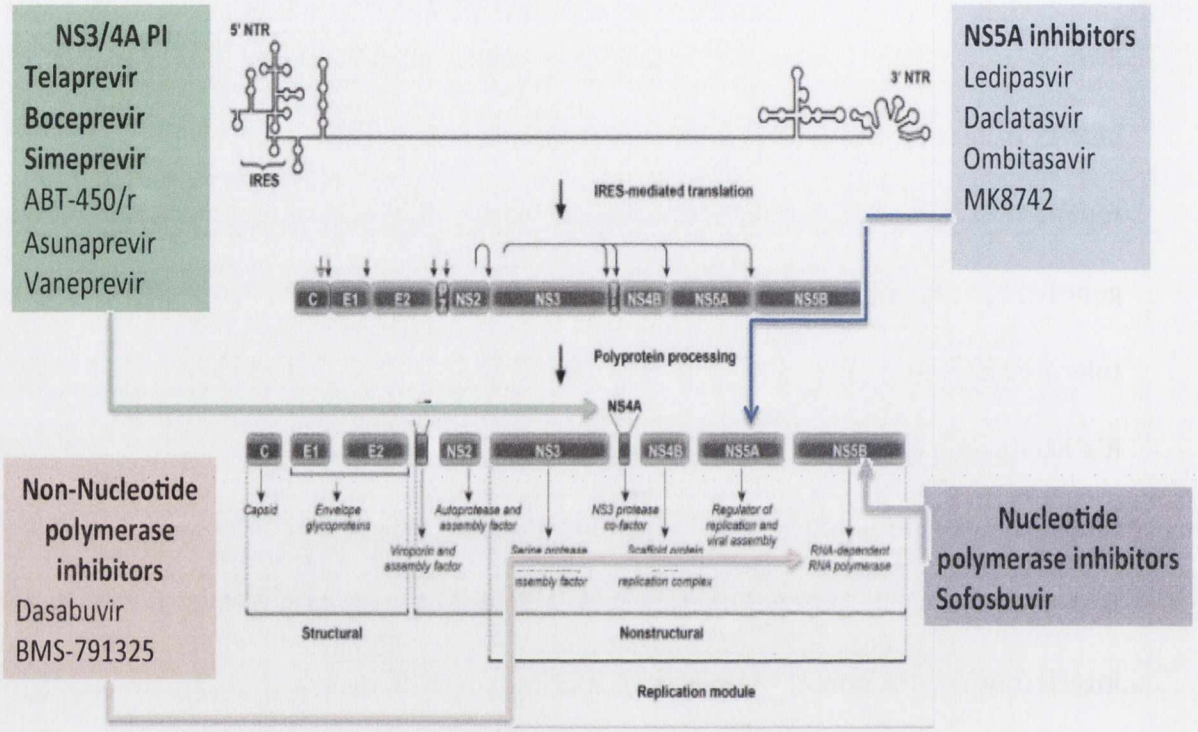



**Figure 2-17 Structure of the HCV polyprotein; the drug classes and sites of action of direct-acting antiviral treatments**

*NS3: Serine protease and helicase assembly factor; NS4A: NS3 protease co-factor; NS5B: RNA dependent RNA polymerase; NS5A: Regulator of replication and viral assembly Adapted from Dubuisson et al (14)*

### 2.6.4 Cost and Efficacy of Second Generation HCV DAAs

A summary of selected clinical trials are presented in Table 2-3. It is clear from the multiple regimens displaying SVR rates in excess of 90% that the new generation of Direct Acting Antivirals (DAA) give a dramatic improvement in efficacy over the first generation PIs. They also display robust improvement in outcomes for patients with non-Genotype 1 infection and advanced fibrosis, although some patients with

advanced fibrosis or previous null-response may still require the addition of ribavirin or prolongation of treatment to 24 weeks (93, 103).

However, the cost of these agents has led to budget impact implications in all health care systems (104). Given that the cost of 12 weeks of simeprevir plus sofosbuvir approaches $150,000, many health-insurers in the US have limited re-imbursement to those patients with advanced fibrosis (105). The cost of 12 weeks of the combination of sofosbuvir plus ledipasvir in Ireland is likely to be in the region of €50,000 . This will require some degree of prioritisation on the basis of clinical need, to allow access to these medications for those who most urgently require them, while containing the budget impact in the medium to short-term. 2015 will see the entrance into the market of more competition, with new agents from Abbvie and other manufacturers. The impact this will have from a pricing perspective is yet to be elucidated.

**Table 2-4 Summary of Clinical trial characteristics and SVR rates from selected trials of next generation DAAs**

| Regimen | Population | F4 (%) | N | Weeks | SVR |
|---|---|---|---|---|---|
| SOF +PR | TN G1 | 17 | 292 | 12 | 89% (80% F4) |
| SOF + RBV | TN (TE) G2 | 15 | 73 | 12 | 97% (90%) |
| | TN (TE) G3 | 24 | 250 | 24 | 94% (79%) |
| SOF + LDV | TN G1 | 16 | 244 | 12 | 99% (94% F4) |
| (ION) | TE G1 | 20 | 220 | 12 | 94% (86% F4) |
| | TE G1 | 20 | 220 | 24 | 99% (100% F4) |
| | TN G1 | 0 | 215 | 8 | 94% |
| SOF + DCV (+/- | TN G1 | 13 | 82 | 12 | 99% |
| RBV) | TE G1 | 22 | 41 | 24 | 100% |
| | TN G2/3 | 11 | 54 | 24 | 93% |
| SOF + SIM | TE G1 | 0 | 80 | 12 | 96% (+RBV) |
| | TE G1 | 50 | 87 | 12/24 | 93-100% |
| "3D" + RBV | TN G1 | 0 | 473 | 12 | 96% |
| | TE G1 | 0 | 394 | 12 | 96% |
| | TE G1 | 100 | 380 | 12/24 | 92-96% |

*Abbreviations: SOF = Sofosbuvir; PR = Pegylated Interferon + Ribavirin; LDV = Ledipasvir; DCV = Daclatasavir; SIM = Simeprevir; 3D = Paritaprevir/Ritonavir + Ombitasavir + Dasabuvir; TN = Treatment Naïve; TE= Treatment Experienced; G= Genotype; F4 = Metavir Fibrosis Stage 4; SVR = Sustained Virological Response (Sources: Kumar et al. (92) and Welzel et al. (93))*

## 2.7 Conclusion

HCV is an infectious disease epidemic of global concern. It is currently undergoing transformational change in its therapeutics with the advent of new drugs and drug-drug combinations every quarter. The cost of these agents, ensure that funding them will be challenging in the current fiscally constrained environment. To fully assess the cost-utility of the new HCV agents, Irish data on the demographics of HCV patients, their Health-related Quality of Life and the cost of untreated HCV will be required. It is a dynamic time to be working in the area of HCV and the arrival of all-oral treatment regimens with limited side-effects raises the possibility of disease eradication, if they are found to be cost-effective and affordable treatment options.

# Chapter 3

# 3 Health Economic Assessment

## 3.1 Introduction

Health Economic assessment has been defined as *"the comparative analysis of alternative courses of action in terms of both their costs and consequences"(106).* Therefore it involves the identification, measurement, valuation and comparison of costs and consequences associated with a particular health investment decision where there are competing options. In the setting of a fixed budget, the investment into any health-care programme results in a failure to invest in another area of health. This is termed the "opportunity cost" and is an important consideration in the decision to invest in any health-care programme. Ideally, the health-care budget would be spent in a way that maximises the health benefits across the whole population. The framework of health-economic assessment allows for robust and transparent comparison of the relative values of competing health-care programmes. It does this with the aim of providing unbiased evidence-based guidance to decision makers in relation to the value of a particular health intervention and the uncertainty around that decision (106, 107).

There are different types of health economic analysis undertaken, which are differentiated and defined largely by the differences in the way they value outcomes (106, 108). The preferred method of health economic assessment in Ireland is cost-utility analysis (109).

## 3.2 Forms of Health Economic Assessment

### 3.2.1 Cost-Utility Analysis

Cost-utility analysis typically values the consequence of a health intervention using a metric that combines the quantity of life with the health-related quality of life (HRQOL) generated by the intervention. The most widely-used unit is the quality-adjusted life year or QALY. It is a generic outcome measure that allows comparison of outcomes across different technologies

and areas of health-care (106-110). This form of analysis is considered the gold standard for conducting economic analysis and is recommended by expert and consensus groups (111)

### 3.2.2 Cost-Effectiveness Analysis

Cost-effectiveness analysis values the consequences of a health intervention in terms of natural units e.g. life-years gained, blood pressure reduction in mmHg. It can be used if the technologies under consideration share a common outcome measure. It may be useful if the decision maker has a fixed budget and is deciding between competing programmes within a health area e.g. different blood pressure lowering strategies. It does not take into account the health-related quality of life of the intervention and does not allow comparison of health benefits across different domains of health with different natural units of outcome measures (e.g. cannot compare mmHg reduction with SVR) (106, 109).

### 3.2.3 Cost-Minimisation Analysis

If the outcomes of the interventions in question are judged to be equivalent, then the main consideration becomes the cost of the interventions. This type of analysis is known as cost-minimisation analysis. It occurs rarely in practice as new interventions requiring assessment usually demonstrate increased efficacy but at an increased cost. There is usually considerable uncertainty in relation to costs and effectiveness which also limits the a priori use of this methodology. It is likely to only be applicable when considering very closely related technologies which have been proven to have the same health outcomes (106, 107, 109).

### 3.2.4 Cost-Benefit Analysis

In cost-benefit analysis the outcomes of interest are displayed in monetary terms. While it may be argued that this is the most explicit method of health economic evaluation, it is rarely undertaken due to difficulties in adequately valuing health outcomes in terms of monetary units (106, 109).

## 3.3 Inputs required for Cost-Utility Analysis

### 3.3.1 Efficacy

In order to accurately compare the cost-utility of the treatments under consideration, there must be evidence of the relative efficacy of one to the other. Ideally, this evidence would be drawn from head-to-head randomised controlled trials to minimise bias. This evidence base is not always available and in those situations it is appropriate to perform an indirect comparison in order to derive relative efficacies. This is a specialised form of meta-analysis which seeks to collate evidence from different sources and develop an indirect comparison network to allow conclusions on the relative efficacies of treatments that have not been directly compared. It is a technique that has become more widespread and guidelines are available to direct best practice in its methodology and reporting (107, 112).

There is an increasing trend for Phase 3 regulatory studies in HCV to be performed without a standard of care comparator arm (3, 4, 6). This leads to challenges with performing network meta-analysis and HTA as comparative efficacy is required to inform both of these processes. A number of approaches have been suggested to overcome these challenges, which tend to occur in disease areas such as HCV, where therapeutics is evolving rapidly and/or there is high unmet clinical need. In general, naïve comparisons across trials are discouraged as they do not adequately consider between-trial variability.

One approach is that of "benchmarking", where the comparative efficacy of the new therapy is compared against the pooled efficacy of multiple historical controls. The pooling of multiple historical controls allows for the creation of a bayesian distribution of responses to account for within and between-trial variability. A response rate can then be set to establish the level of response a new drug would need to achieve in order to be considered significantly different to the historical control.

Matching-adjusted indirect comparison is another technique that has been suggested in this scenario. This involves propensity-score matching the baseline characteristics between two trials to adjust for between-trial variability. The outcomes are then compared across balanced populations. This technique requires individual patient-level data for one of the comparators which may not be freely available to an academic researcher (113).

These techniques are most effective where the populations in the included studies are relatively homogenous and the outcome of interest and potential confounders are common to the historical and current comparator. This is broadly-speaking the case in HCV clinical trials so it should be possible to derive the relative efficacies of the newer DAAs as part of a future research direction.

### 3.3.2 Cost of Illness and treatment

As the basic principle in economic analysis is the comparison of costs and consequences it is clearly important to have robust and accurate cost input data (106, 107, 114, 115). In a Markov model it is necessary to have cost information about the cost of remaining with the illness in question versus without the illness, in addition to the cost of the intervention. There are two broad approaches to cost studies, micro-costing and macro-costing (115, 116). Using a micro-costing approach is labour intensive but results in more accurate results as it allows quantification and valuation of each unit of resource used. While it is more accurate, it presents difficulties with its generalisability outside of the setting where it was performed. The strengths of micro-costing lie in the richness of the clinical data which allows accurate stratification of cost by disease severity and it is likely to be more reflective of true costs in a disease area where practice is rapidly changing (117). With a macro-costing approach, data on resource use is derived from large, generally administrative, databases and a valuation on that resource use is applied. The Diagnostic Related Group system (DRG) would be an example of this system (117). The advantage of this approach is that it is more generalisable and less

resource intensive, however it may underestimate costs in areas of healthcare where practice is rapidly changing and it relies on accurate coding of clinical episodes (114, 116, 117).

### 3.3.3 Health-state utility values

In cost-utility of analysis, consequences are valued using a generic measurement unit. This is most commonly the QALY (106, 107, 109, 111). Patient-derived descriptions of health-related quality of life can be generated using generic questionnaires such as the Euroqol 5-Domain (EQ-5D) or Short Form 36 (SF-36) (109, 118, 119). A numeric score is then applied to these descriptions using society-derived preferences for health-states displaying those particular features (120). This numeric score is representative of the QALY value attached to that health-state and is termed a "utility". To perform a cost-utility analysis it is necessary to have information about the utility values associated with health-states present in your analysis (106, 110). Ideally, these would be derived from a representative sample of the population for whom the treatment is being considered, but if this data is not available it may be appropriate to take values from a similar population reported in the literature (109).

### 3.3.4 Population Demographics

The population to be studied may have characteristics that will affect the outcome of the model. For instance, if the population entering the model is older a shorter time horizon may be appropriate and they will have higher rates of background mortality than a younger cohort. Similarly, gender will have an impact on life expectancy and background mortality. Therefore it is important to have accurate information on the baseline demographics of the population to be modelled in order to account for differences in background events and in some cases, differences in response to treatments (108-110).

## 3.4 Modelling of outcomes in Cost-utility Analysis

### 3.4.1 Types of Model

*Decision Trees*

Decision trees are the simplest form of economic model where outcomes of treatments are compared against each other over a single defined time period and the costs and consequences of individual strategies are calculated for the intervention. It commences with a decision node which represents the decision point between competing strategies. Subsequent to the decision node, possible events are represented by chance nodes. Pathways are the potential routes through the decision tree that a patient may make. The likelihood of entering a particular pathway is based on the probability of an event occurring. Probabilities in individual pathways are conditional on the probabilities that have already occurred. Patients accumulate the sum of the costs they accrue along a particular pathway. The eventual likelihood of completing a particular pathway is the product of the individual probabilities along the pathway. Decision trees are useful for displaying decisions on interventions that occur once and have limited possible chance events. If there are multiple different consequence events the decision tree rapidly becomes very "bushy" and unwieldy and may be difficult to program and present. The other limitation is that the time the decision tree represents is not explicit. For modelling chronic diseases with multiple consequences over long time periods, a Markov model is a more appropriate approach (108, 110).

*Markov Models*

Markov models are used when costs and consequences need to be calculated over a longer time period, typically a life-time. This is important when modelling the impact of interventions to mitigate the effects of chronic disease. They allow easier modelling of competing risks of death such as background mortality when compared to decision trees. This becomes important as the population in question ages. The model is run in cycles with patients in the model transitioning from mutually exclusive health-state to health-state in accordance with

typical disease progression. They accrue the costs and QALYs associated with the health-state they are in at each cycle of the model. There are some limitations of Markov models. The costs and QALYs gained are applied at the end of each cycle so that patients that die at some point in that cycle accrue the full values of that cycle, which may not be representative. To better approximate the continuous nature of time, half-cycle correction is employed to create the assumption that the transition occurs in the middle of the cycle rather than the end. A core limitation of Markov models is that they have no "memory". The probability of transitioning from one health-state to the next at Cycle *n* is entirely dependent on the transition probability at that point and does not take into consideration prior events. In some diseases, patient's response to treatment may be dependent on their past history of treatment. This is difficult to build into Markov models but can be overcome with the use of tunnel states or tracker variables that account for prior treatment history (107, 108, 110).

### *Hybrid Decision Tree-Markov models*

Hybrid models combine an initial decision tree structure examining different treatment strategies with a Markov model which examines patient costs and outcomes over the longer term. The structure of the Markov model that patients enter is based on their path through the decision tree. They accrue the costs and QALYs applicable to the arm of the decision tree that they travel through and then the costs and QALYs gained over the longer time horizon with each cycle of the Markov. This model structure is useful to examine treatment strategies and costs that occur once but have longer term implications for chronic disease mitigation.

### *Discrete Event Simulation (DES)*

Discrete Event Simulation is used when it is necessary to model the effect of an individual on the larger population or to assign a particular treatment history and response based on that history to an individual. It is frequently used for modelling communicable diseases where the

host-herd interaction is of importance. It is a very flexible form of modelling whose main disadvantage is the computational burden it requires (108).

## 3.5 Presentation of results and uncertainty

### 3.5.1 Cost-Effectiveness Plane and Incremental Cost Effectiveness Ratios (ICERs)

Results of economic analysis are generally plotted using the cost-effectiveness plane (CE plane). This compares incremental costs on the Y-Axis to incremental effectiveness on the X-Axis. *(Figure 3-1)* The Quadrants are labelled 1-4. Most new technologies fall into Quadrant 1 i.e. they usually have an effectiveness gain with a corresponding increase in price. Technologies that are plotted in Quadrant 4 cost more and are less effective than standard of care and would generally not be considered. Occasionally new technologies cost less and are more effective (Quadrant 2) or they are less effective but cost less (Quadrant 3). Technologies in Quadrant 2 are always considered cost-effective and those in Quadrant 3 may be worth considering in the setting of budget constraints (106, 107, 109, 121). The incremental cost effectiveness ratio can be calculated by dividing the incremental increase in effectiveness of one therapy over another therapy by the incremental cost of one treatment over another e.g.

$$\text{ICER} = \frac{E_2 - E_1}{C_2 - C_1}$$

where $E_2$ is the effectiveness and $C_2$ the cost of Treatment 2 and $E_1$ is the effectiveness and $C_1$ the cost of Treatment 1.

The CE plane can also be used to display the willingness to pay threshold. This is the arbitrary threshold at which a technology is felt to represent value for money (106, 110). The 2012 Irish Pharmaceutical Healthcare Association (IPHA)-Department of Health Agreement set the threshold ICER at €45,000/QALY (122) although not all technologies that have ICERs below €45,000/QALY are automatically reimbursed and some technologies with ICERs above this

threshold have been reimbursed when it was felt that it was warranted because of their innovative nature or the clinical need that they addressed (123, 124).

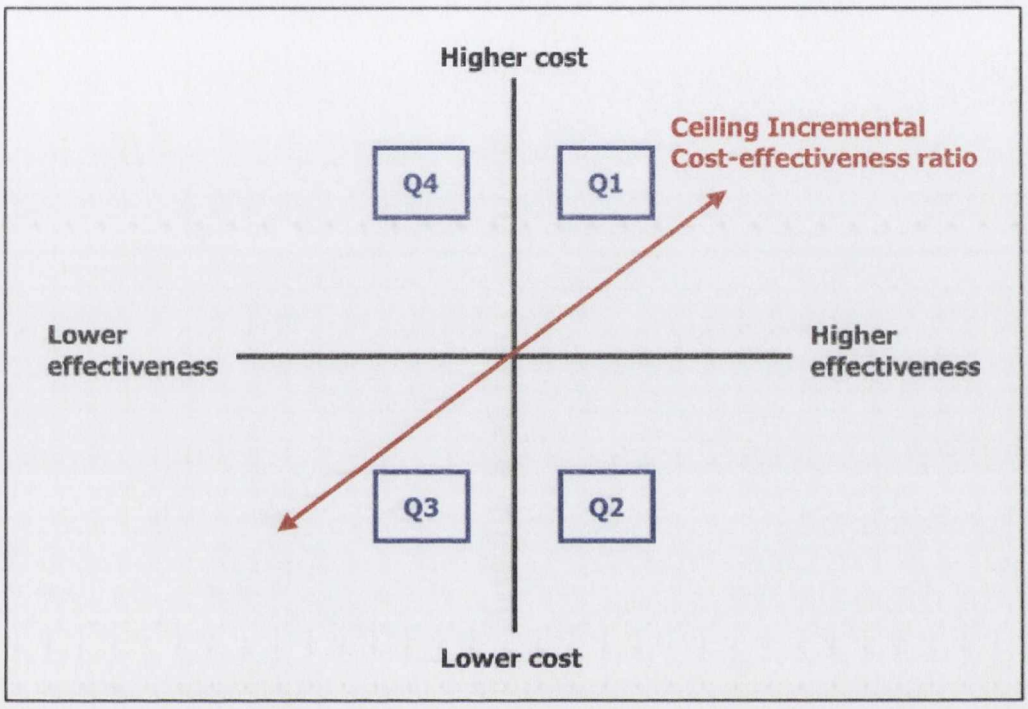
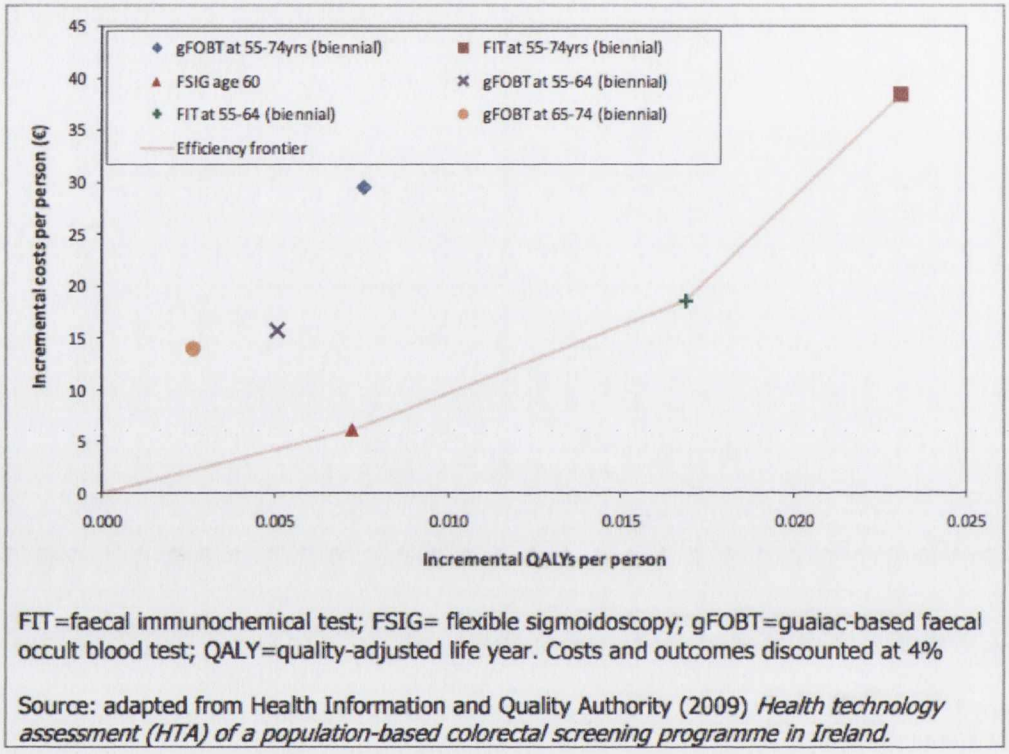



**Figure 3-1 Cost-Effectiveness Plane**
*HIQA 2014* (109)

As previously mentioned, most new technologies fall in Quadrant 1 demonstrating that they are progressively more effective but more costly than the previous standard of care. Occasionally other scenarios are seen, especially when multiple comparisons are performed. In some situations, a comparator may be more costly but less effective than another comparator. In this scenario, the first comparator would never be considered as the most cost-effective option and it is described as being "dominated". Another situation that can arise, is one where although each comparator demonstrates increasing effectiveness for an increasing cost when compared against each other, a combination of other options can provide a higher level of health benefit for the same cost than a particular option alone. In this case, the option that is discounted is considered to be subject to "extended dominance" (106, 125). Figure 3.2 displays

an example of a cost-effectiveness plane with strategies that are subject to dominance. In this figure guaic-based faecal occult blood testing lies above the efficiency frontier and is dominated by strategies that employ flexible sigmoidoscopy or faecal immunochemical testing (109).




FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%

Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

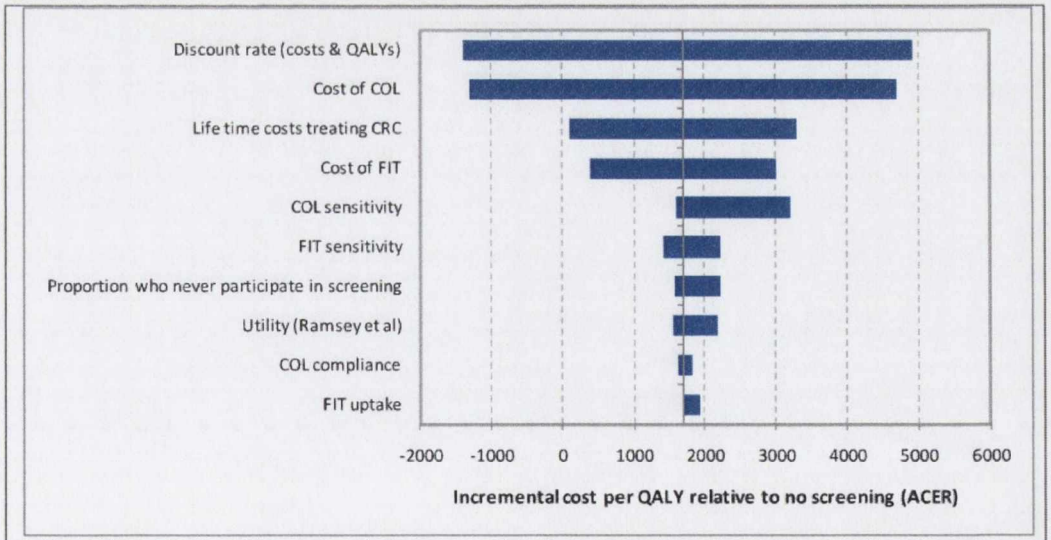
**Figure 3-2 Example of Cost-effectiveness plane with cost efficiency frontier**
*HIQA 2014* (109)

### 3.5.2 Deterministic and One-way sensitivity analysis

Economic evaluations can be calculated using point-estimate values of the costs and consequences being considered. This is usually the mean value for the variable of interest and analysis conducted in this way is termed *deterministic.* The mean ICERs generated by the competing alternatives can be plotted on the CE plane and a line drawn between which represents that *efficiency frontier.* Based on the willingness to pay threshold, the optimal

choice i.e. the strategy which provides the most health gains at that threshold, can be identified *(Figure 3-2)*.

It is important that the uncertainty around those point estimates be analysed and reported. At a minimum this is done with a probabilistic sensitivity analysis, where a random value from a range of values is chosen for each variable with each iteration of the model and the model is run over a large number of iterations. This allows a calculation of the overall uncertainty of all the variables in the model. A one-way sensitivity analysis is used to determine the impact of specific parameters on the deterministic ICER. In this form of analysis the point estimate value of an individual variable is varied between a realistic low and high value and the effect this has on the ICER is examined and presented. Variables that have the most effect on the overall results of the model when varied under one-way sensitivity analysis may be presented graphically in the form of tornado diagram (106, 107, 109, 110). *(Figure 3-3)*




COL=colonoscopy; CRC=colorectal cancer; FIT=faecal immunochemical test; QALY=quality adjusted life year.

Source: Adapted from Health Information and Quality Authority (2009) *Health Technology Assessment (HTA) of a population-based colorectal screening programme in Ireland.*

**Figure 3-3 Example of a Tornado diagram**
*HIQA 2014* (109)

### 3.5.3 Probabilistic Sensitivity Analysis (PSA)

Probabilistic sensitivity analysis attempts to account for all the uncertainty in variables used in the model. Rather than mean values for the variables, a random value is taken from a plausible range of values for each variable. The distribution chosen for the ranges depends on the type of variable. The model is run through a large number of iterations with different random samples of every variable used in each iteration. The costs and effectiveness generated with each iteration are then averaged to give mean values for the total costs, QALYs and ICERs. The spread in the values generated can be represented graphically in a scatterplot (107, 110). *(Figure 3-4)*

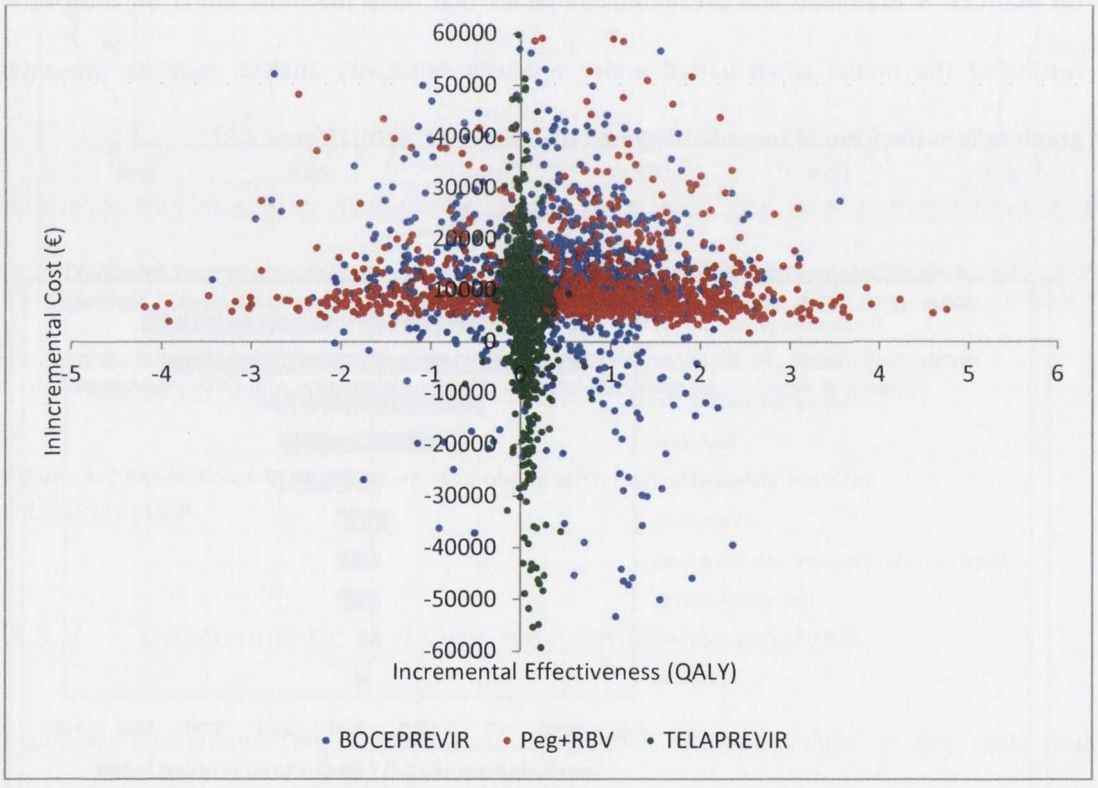



**Figure 3-4 Example of PSA Scatterplot of Incremental ICERs of Peg-IFN + RBV versus No Treatment, Boceprevir versus Peg-IFN +RBV and Telaprevir versus Boceprevir**
*(Source: Chapter 8)*

The distribution of the scatterplots can be further analysed using 95% ellipses. These are a form of scatterplot which display the scatter of the values from the PSA with their 95% confidence interval and the quadrant that they fall into. This can be useful in explaining and interpreting the shape, y-axis intersection and asymptote of the cost-effectiveness acceptability curve (CEAC) (121, 126). The CEAC is constructed by plotting the proportion of the cost and effect pairs that are the most cost-effective at a range of threshold values. It shows the probability that an intervention is cost-effective given the data. *(Figure 3-4)* It does not necessarily identify the optimal strategy from a net benefit perspective at a particular threshold (121, 125, 126). In certain situations it is possible that the option with the highest probability of being cost-effective option on the CEAC would not deliver the greatest health benefit. (125). To fully answer the question of the optimal strategy from a net benefits perspective, a cost-effectiveness frontier (CEAF) needs to be constructed. This plots the strategy that delivers the greatest net benefit at a particular threshold (125). In Figure 3-5 below a CEAC is compared to the same data plotted as a CEAF.

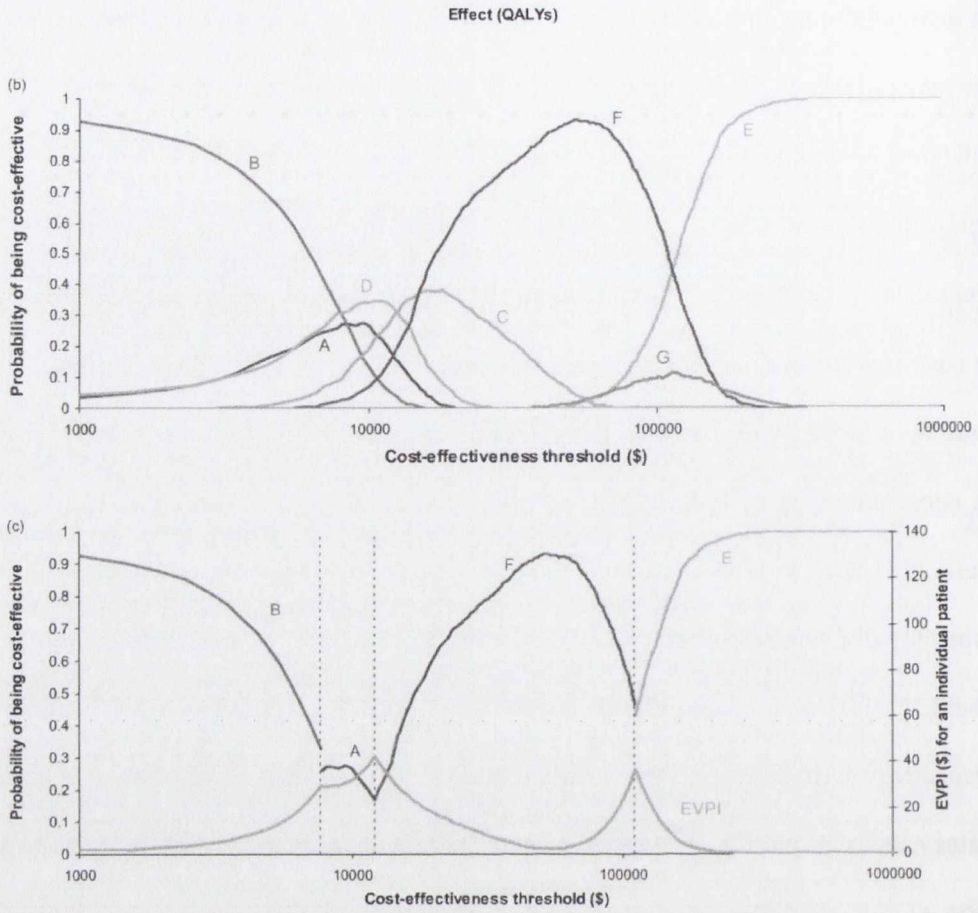



**Figure 1** Replication of the analysis by Goeree et al. [1]. Results are presented in terms of the cost-effectiveness plane (a), cost-effectiveness acceptability curves (b), and the cost-effectiveness acceptability frontier and the expected value of perfect information (EVPI) (c).

**Figure 3-5 Example of Cost-Effectiveness Acceptability Curve and Cost-effectiveness Acceptability Frontier**
*Barton et al 2008* (125)

## 3.6 Health Technology Assessment in Ireland

The rational allocation of health resources is of paramount importance at all times but especially in a time of fiscal constraint. The health budget in Ireland rose from 5.7 billion in 2000 to 15.4 billion in 2009. Since 2009 the overall budget for health has reduced and in 2013 it was €14.1 billion. This represents a 36% increase in health spending from 2004 to 2013 (127). *(Figure 3-6)* The National Centre for Pharmacoeconomics in Ireland (NCPE) was

established in 1998 to ensure the cost effective use of resources in relation to the pricing of new high-cost pharmaceutical agents. It's role has expanded since 2009 with all new medicines requiring evaluation and those deemed to be high-cost or to have a significant budget impact reviewed through a formal health-technology assessment (HTA) procedure (123, 124, 128).

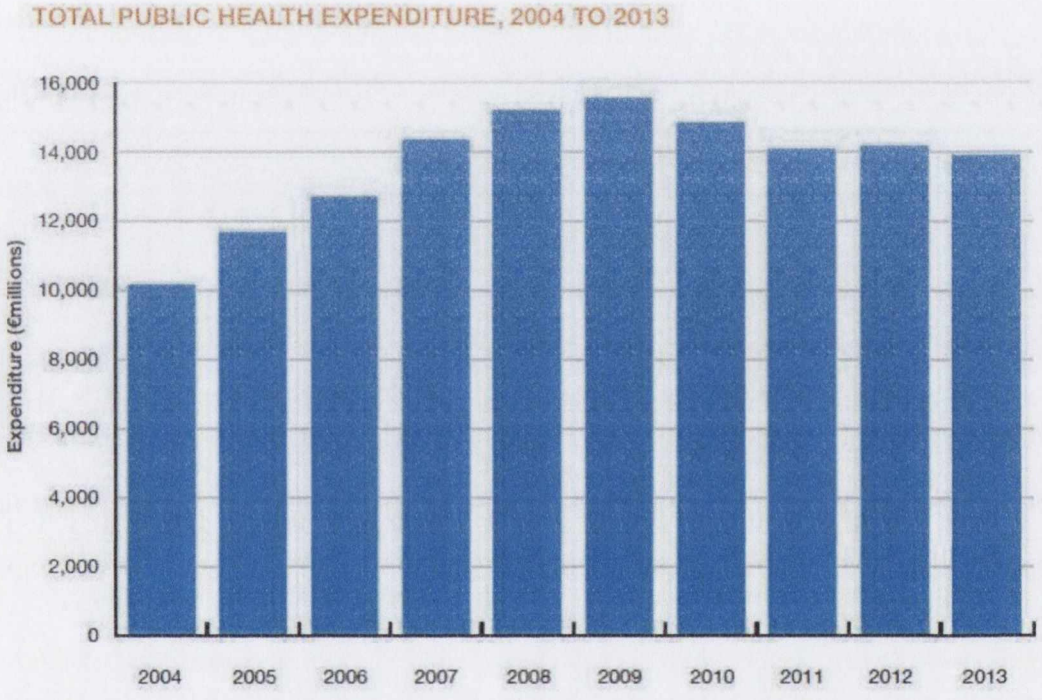



**Figure 3-6 Total Public Health Expenditure from 2004 to 2013**
*Dept of Health 2014* (127)

### 3.6.1 National Centre for Pharmacoeconomics

The NCPE was established in 1998 with funding from the Department of Health and Children. The aim of the centre is to promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education (128). In 2006, a formal requirement for evidence of cost-effectiveness in reimbursement decisions was introduced with pharmacoeconomic evaluation of high-cost items undertaken by the NCPE at the request of the Corporate Pharmaceutical Unit of the Health Service Executive. Since 2009, all new medicines are assessed following receipt of an application for reimbursement under the

community drug scheme (123, 124). The majority undergo rapid review and are then put forward for reimbursement. High-cost items or those with significant budget impact undergo full HTA. If the product is referred for HTA the companies are required to submit a dossier of evidence to support the effectiveness and cost-effectiveness of the treatment in question. The NCPE undertakes to complete rapid reviews within 2-4 weeks and HTA within 90 days (128). The 2012 HSE-IPHA agreement established a cost-effectiveness threshold of €45,000/QALY although as mentioned previously, not all medicines are automatically reimbursed below this threshold and some are reimbursed above this (122).

In 2013, the NCPE received thirty-nine rapid reviews and recommended fifteen full HTAs. Twenty-one full submissions were received and ten HTAs were completed within the year. After HTA, there was a negative decision for re-imbursement in nine cases and a positive recommendation for reimbursement in 2 cases. To date, there have been fifty-two rapid reviews received in 2014. Figure 3-7 summarises the numbers of rapid reviews and full submissions to the NCPE from 2012 to December 8th 2014.

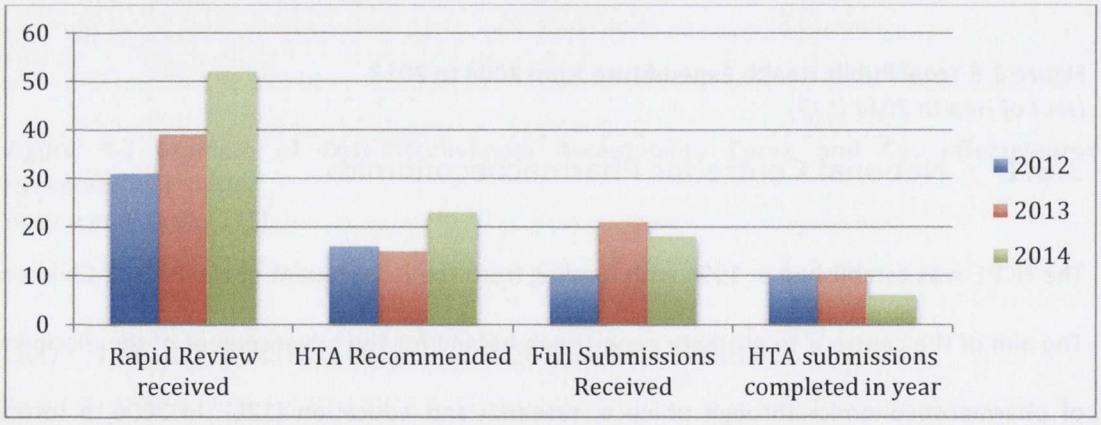



**Figure 3-7 Summary of NCPE rapid reviews and health technology assessments 2012-2014**
*Personal Communication, NCPE December 2014* (129)

### 3.6.2 Reimbursement of Medicines in Ireland

There are a number of different reimbursement schemes in Ireland that are known collectively as the Community Drugs Schemes and are administered through the Primary Care Reimbursement Service (PCRS). These comprise of the General Medical Services (GMS), the Drug Payment Scheme (DPS), the Long Term Illness Scheme (LTI) and the High-Tech Drug Scheme (130). Prior to inclusion on the community drug scheme, a drug must apply for and receive a positive recommendation for reimbursement (124). Expenditure on the Community Drug Scheme increased exponentially between 1991 and 2009, leading to concerns about the sustainability of the scheme in the absence of active management (123, 124). In 2013 the HSE's drugs budget exceeded €1.8 billion under the Community Drug Schemes (131). *(Figure 3-8)*

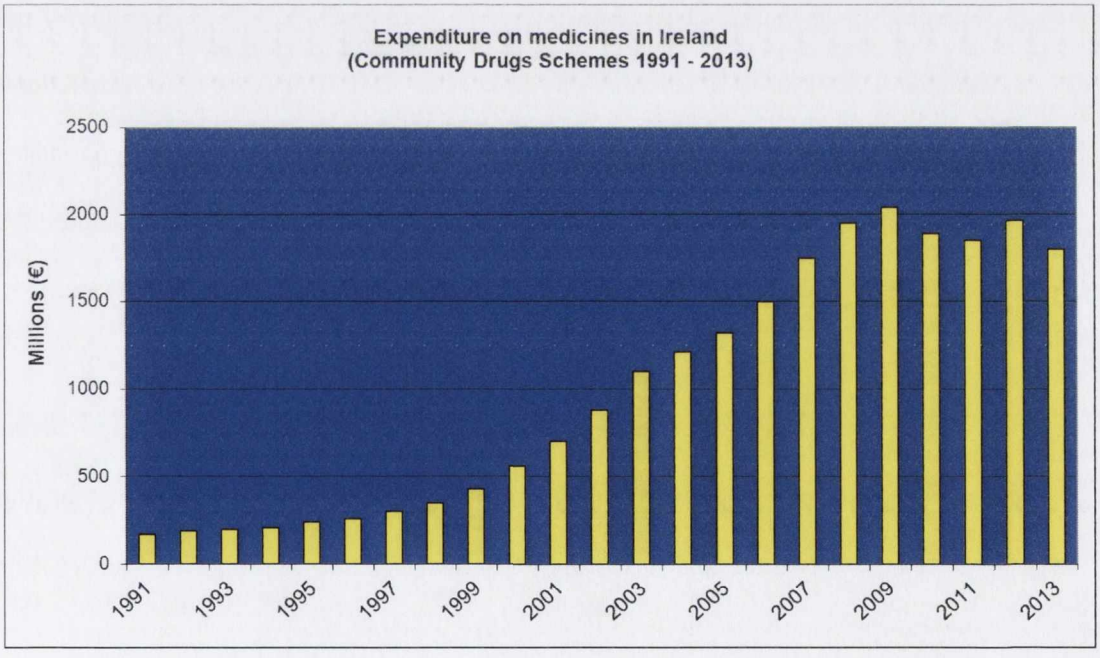



**Figure 3-8 Expenditure on Medicines in Ireland under the Community Drug Schemes 1991-2013**
*Reproduced with the permission of Dr. M Barry, Source: HSE-PCRS Annual Reports 1991-2013* (131)

The GMS scheme comprises of patients with a medical card. This is a means tested scheme which provides general practitioner, medical and surgical care to people who could not arrange such services for themselves or their dependents without undue hardship. Drugs, medicines and appliances approved under the scheme are dispensed through community pharmacies. In 2012, 1.8 million people held a medical card, which is almost 41% of the total population and represents a 60% increase in numbers since 2005. Since December 2013, a co-payment of €2.50 per prescription item subject to a limit of €25 per family per month has been introduced. Analysis of reimbursement data from the PCRS would show that while expenditure on the GMS has been relatively stable or slightly increased since 2008 *(Figure 3-9)*, the increase in the number of eligible persons has resulted in a reduction in the amounts spent per person *(Figure 3-10)* (130).

The Drug Payment Scheme is a co-payment scheme used to supply prescription items to people who are not in receipt of a medical card. Once a threshold of €144 per family per month has been reached, the DPS provides payment to the Pharmacist for prescription items in excess of this amount. Since 2010, the numbers of people availing of the DPS has fallen along with the overall cost of the scheme and the average payment per claimant. *(Figure 3-9 and 3-10)* (130).

The Long Term Illness Scheme provides necessary drugs or appliances without charge, regardless of income, to people with defined chronic illnesses. Overall expenditure on this scheme has fallen since 2008 as has the average cost per claimant. *(Figure 3-9 and 3-10)* (130)

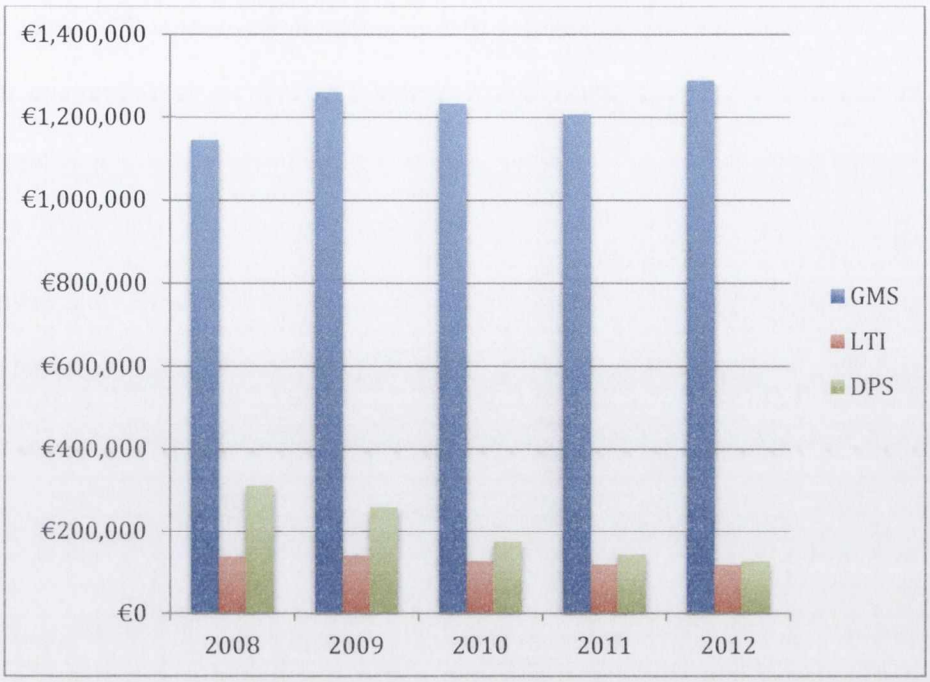



**Figure 3-9 Overall Expenditure on Medications dispensed under the GMS, DPS and LTI schemes 2008-2012**
*HSE-PCRS Annual Reports 2008-2012* (132)

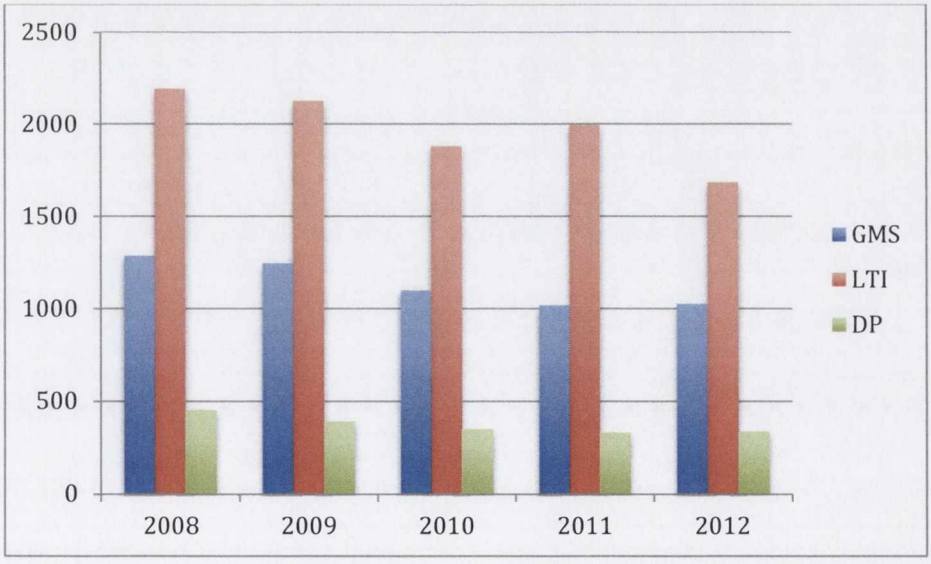



**Figure 3-10 Average cost per patient on the GMS, DPS and LTI schemes 2008-2012**
*HSE-PCRS Annual Reports 2008-2012* (132)

The High-tech drug scheme (HTDS) was established in 1996 to provide payment to Pharmacists for high-cost items prescribed from the hospital services but dispensed in the community. It was developed to facilitate dispensing for certain high cost drugs in the areas of oncology, multiple sclerosis and transplantation drugs but has expanded exponentially since its inception. Re-imbursement for pegylated interferon and ribavirin treatment for HCV has been administered through this scheme. The cost of the HTDS in 2012 was €405 million. Figure 3-11 displays the overall expenditure on the scheme from 2005 to 2012 (124, 130).

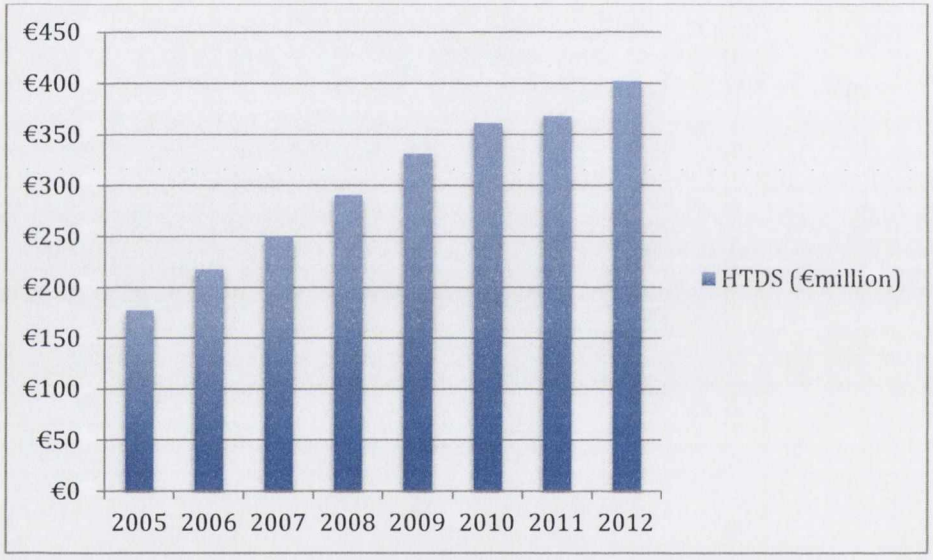



**Figure 3-11 Overall Expenditure on the High-tech Drug Scheme from 2005-2012**
*HSE-PCRS Annual Reports 2005-2012* (132)

### 3.6.3 Medicines Management Programme

The Medicines Management Programme was established in 2013 to provide national leadership in relation to prescribing quality, access to medicines and expenditures on medicines. It is headed by the National Medicines Information Centre, the NCPE and the HSE-PCRS and aimed to secure €20 million in savings in 2013 and 2014 without impacting on frontline health services and while ensuring that patients continued to have access to essential medications. It also aimed to enhance evidence-based, generic prescribing and optimise

patient safety through a reduction in medication–related adverse effect. It has initiated a number of strategies in order to achieve these aims (133).

### *Preferred Drugs Initiative*

The *"Preferred Drugs Initiative"* identifies a single preferred drug within a therapeutic class and encourages prescribers to make this the drug of first choice when prescribing for a particular condition. The preferred drug is selected following an evaluation of the clinical efficacy and effectiveness data, dosing and administration, side-effects, cost and national and international guidelines. To date, preferred drugs have been identified in a number of therapeutic areas (133). Table 3-1

**Table 3-1 Therapeutic classes of medications considered by the MMP and their preferred drug choice**

| Therapeutic Class | Preferred Drug |
|---|---|
| Angiotensin-converting enzyme (ACE) inhibitor | Ramipril |
| Angiotensin-II Receptor Blocker (ARB) | Candesartan |
| Proton Pump Inhibitor | Lansoprozole |
| Serotonin Noradrenaline Re-uptake Inhibitor (SNRI) | Venlafaxine |
| Selective Serotonin Reuptake Inhibitor (SSRI) | Citalopram |
| Statin | Simvastatin |
| Acetylcholine Receptor blockers | Tolterodine extended release |

The introduction of a preferred drug initiative has had an impact on prescribing. Lansoprozole was introduced as the first "preferred drug" in April 2013. There has been an increase seen in the prescriptions of lansoprozole and a decrease in the prescriptions of omeprazole since this time. Although esomeprazole (the most expensive drug in this class) remains the most

commonly prescribed proton pump inhibitor, the growth of its market share stopped with the introduction of the preferred drug initiative. (*Figure 3-12)* It is estimated that €19.5 million in savings could be achieved by prescribers changing prescribing habits when prescribing for patients newly commencing on a drug (131).

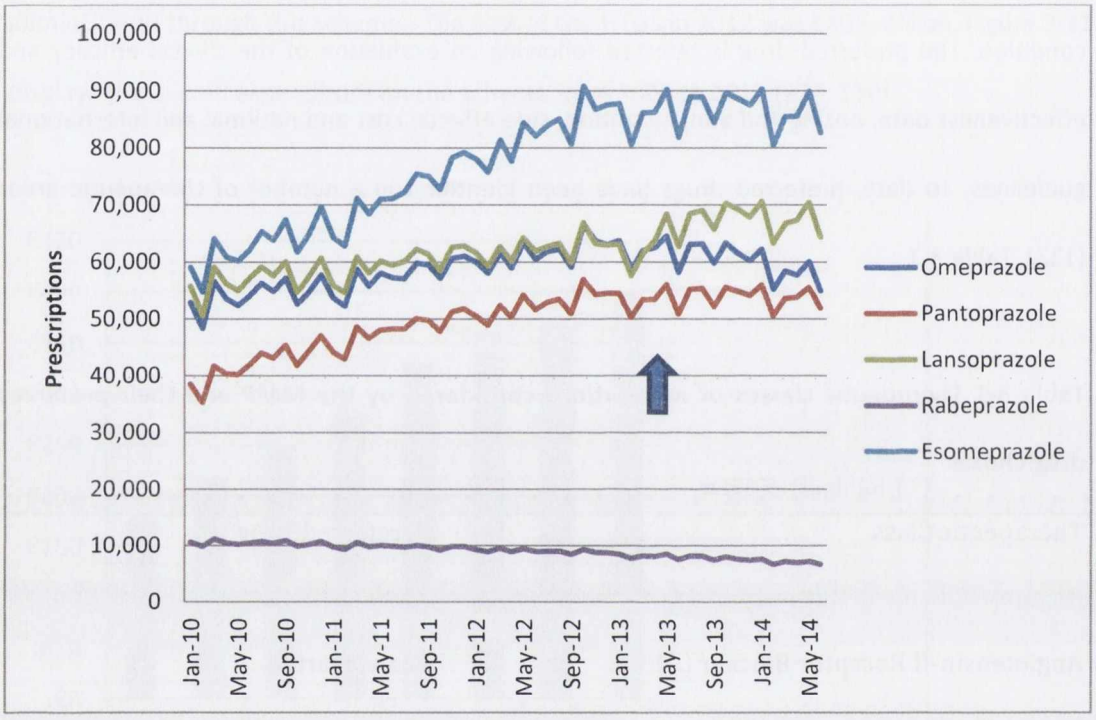



**Figure 3-12 Prescription of Proton Pump Inhibitors (PPI) on the GMS scheme Jan 2010 to June 2014. Blue arrow indicates the introduction of the preferred drug scheme for PPIs**
*Reproduced with the permission of Dr. M Barry, Source: HSE-PCRS reports* (131)

### *Prescribing and Cost Guidance*

"Prescribing and Cost Guidance" aims to increase awareness among prescribers of the costs associated with particular drugs and to encourage prescribers to choose less expensive but equally effective agents for particular conditions. Therapeutic areas that have been targeted to date are inhaler therapies for asthma and chronic obstructive pulmonary disease (COPD) (133).

### *Reference-based Pricing*

The Health Act of 2013 established legislation that allowed pharmacists to provide a generic substitution for a branded product (134). This paved the way for the introduction of reference based pricing in Ireland. In November 2013 the HSE introduced phase 1 reference pricing. With this strategy, the payer sets a price they are willing to pay for a particular branded product and its generics. If a patient prefers to receive the original branded product rather than a generic substitute, they will be required to pay the difference in the price. In practise, many of the original branded products introduce a price reduction to the reference price in order to maintain a market share (131). Atorvastatin was the first drug to be reference priced in November 2013 and esomeprazole was the next in January 2014. These drugs and therapeutic areas were targeted as they had a large budget impact on the GMS scheme in 2012. At over €50 million, atorvastatin was the second most expensive drug in terms of ingredient cost reimbursed under the GMS scheme in 2012. Esomeprazole was the fifth most expensive drug in terms of ingredient cost with an expenditure of €27 million in 2012 (130). Figures 3-13 and 3-14 show the impact on the community drugs budget with the introduction of reference pricing for these agents. In May 2013, €7 million per month was spent on statins. In contrast, €3.5 million was spent in May 2014. The monthly expenditure on PPIs In May 2013 was €6.5 million and in May 2014 was €4.2 million. To date 37 products have been referenced priced (131).

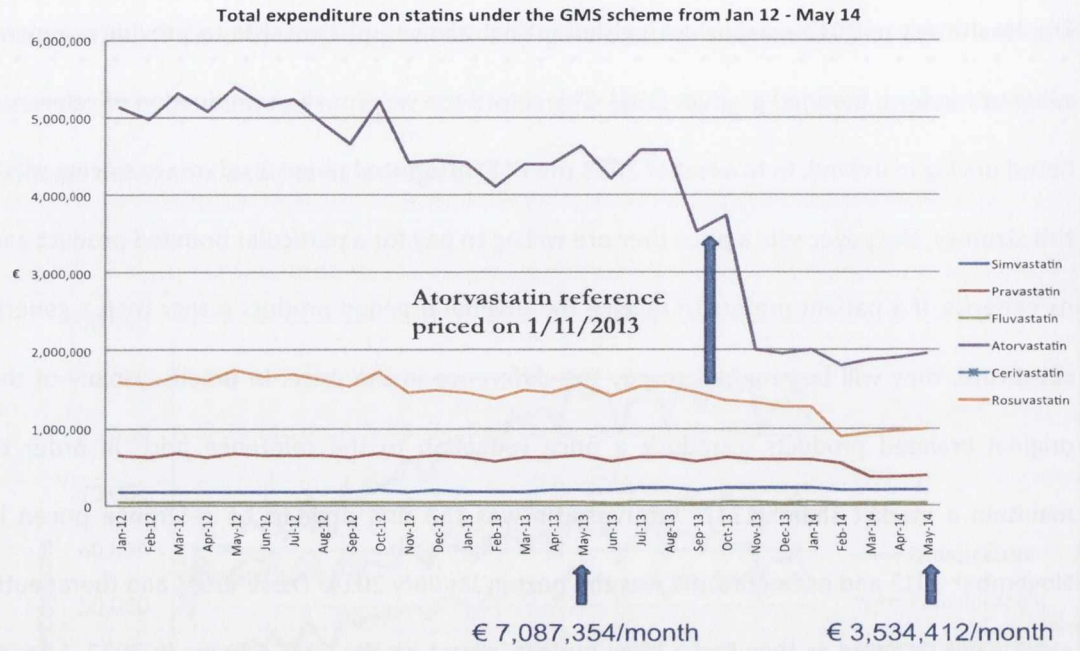



**Figure 3-13 Total Expenditure on statins under the GMS scheme January 2012 to May 2014. Blue arrow indicates commencement of reference pricing for atorvastatin**
*Reproduced with the permission of Dr. M Barry, Source: HSE-PCRS reports* (131)

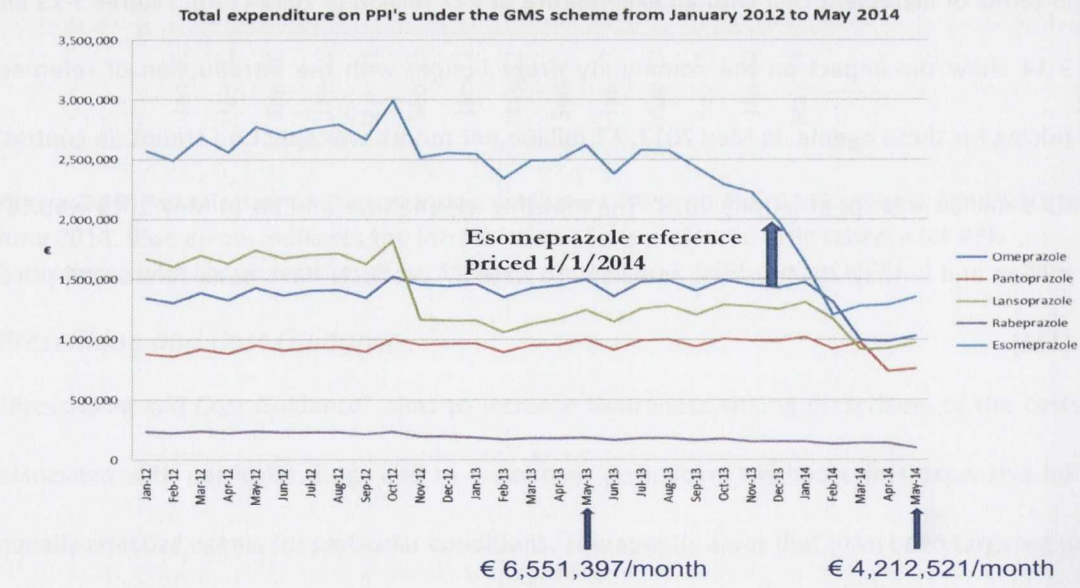



**Figure 3-14 Total Expenditure on Proton Pump Inhibitors under the GMS scheme January 2012 to May 2014. Blue arrow indicates commencement of reference pricing for esomeprazole**
*Reproduced with the permission of Dr. M Barry, Source: HSE-PCRS reports* (131)

## 3.7 Conclusion

There have been many developments in economic evaluation in Ireland since its introduction and it has gained increasing prominence in recent years as the health service aims to maximise the use of scarce resources. The principles and techniques used in economic evaluation allow for a standardised, reproducible and transparent platform on which to base health resource allocation decisions. There have been a number of changes to legislation, regulation and reimbursement of medications in Ireland in the last five years. These have resulted in a modest but important decrease in the Community Drugs Budget at a time when more of the population were reliant on its resources. Rational management of prescribing and the drugs budget will allow future investment into important developing therapeutic areas and without such interventions the cost of medicines in Ireland will rapidly become unsustainable resulting in reduced access to new medicines for Irish citizens.

# Chapter 4

# 4 The Budget Impact of Hepatitis C Treatment in Ireland 2001-2012

## 4.1 Introduction

The initial research undertaken for this thesis aimed to establish the number and characteristics of HCV treatment-experienced patients in Ireland. Their demographics are important to inform the baseline characteristics of the eventual economic model. The cost of HCV treatment to date informs the budget impact of the standard of care treatment. The proportion of patients receiving synthetic growth factor support in the setting of HCV treatment is also important to establish, as this potentially represents a significant additional drug cost of HCV treatment. There has been progress made recently under the auspices of the Irish HCV Outcomes and Research Network (ICORN) and the National HCV strategy in improving the understanding of the HCV epidemic in Ireland (135, 136). However, national estimates of the number of patients who have been treated for HCV, their demographics and the cost associated with that treatment have yet to be published. Establishing such estimates gives a baseline against which to benchmark future treatment endeavours. It also gives an assessment of the capacity of national HCV treatment services that is useful for service planning. At the beginning of this new era in HCV care, we aimed to establish an estimate of the number of HCV patients treated from 2001-2012 and the drug costs associated with that treatment.

## 4.2 Methods

This study was carried out using data obtained from the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. The HSE-PCRS is a national database used primarily to reimburse the provision of health care services and prescription medication in Ireland, through a number of national schemes, including the High Tech Drug

Scheme (HTDS). The HTDS is a community drugs scheme that caters for high cost medicines initiated in hospital but subsequently dispensed in the community. Prescription medications dispensed through the scheme are recorded in the HSE-PCRS database using the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification. The HSE-PCRS database also collates basic demographic information pertaining to each GMS claimant including age, sex and region. It does not, however, contain any clinical diagnosis or outcomes data. Prescriptions for the treatment of HCV infection were identified by searching for co-prescription of pegylated interferon 2α or pegylated interferon 2β along with ribavirin from 2000 to 2012 using the ATC classification codes within the HTDS. The rates of co-prescribing of synthetic anti-anaemics (EPO), and granulocyte colony stimulating factor (G-CSF) were identified using the same methods. The incident number of patients prescribed these medications was established through unique patient identifiers in the database. The costs of these prescriptions were quantified using unit drug costs from the national health payer adjusted for dispensing fees and discounts. As the treatment course for many patients' spanned different calendar years, the prevalence of HCV patients on treatment in a particular year is also presented to accurately reflect clinic capacity. If a treatment course spanned different calendar years, the costs are included in the year that they are accrued e.g. 48 week treatment course commencing in October Year 1 and completing in August Year 2. The cost of 13 weeks of treatment is captured and included in the total costs associated with Year 1 and the costs of 35 weeks of treatment is captured and included in the total costs associated with Year 2. Design of the study and identification of appropriate variables to search for was conceptualised by the author of this thesis. Interrogation of the PCRS database and presentation of the summary statistics from the PCRS dataset was performed by Dr. Kathleen Bennett of the Department of Pharmacology and Therapeutics, Trinity College Dublin. Prescriptions dispensed to patients attending the Hepatitis C clinic based within the Genitourinary and Infectious Diseases (GUIDE) service in St. James Hospital are not captured

through the PCRS database. Therefore, prescriptions dispensed to patients treated through this service were established through interrogation of the pharmacy records in GUIDE and the drug costs associated with their care were calculated. This was combined with the HTDS data to form an overall estimate of patient numbers and cost of drug treatment. Costing and analysis of the GUIDE dataset was performed by the thesis author, as was the amalgamation of the two datasets and analysis of the final dataset. Descriptive statistics are presented as sums, means and 95% confidence intervals. Limited demographic information was available for the PCRS patients. Analysis was performed using SAS v9.3 and Excel.

## 4.3 Results

There were 2398 courses of pegylated interferon and ribavirin administered to 2320 patients between January 2001 and December 2012. Annual prevalent treatment numbers peaked in 2009 with 446 patients receiving HCV treatment. Figure 4.1 displays the annual number of incident and prevalent cases receiving HCV treatment that occurred from 2001-2012.

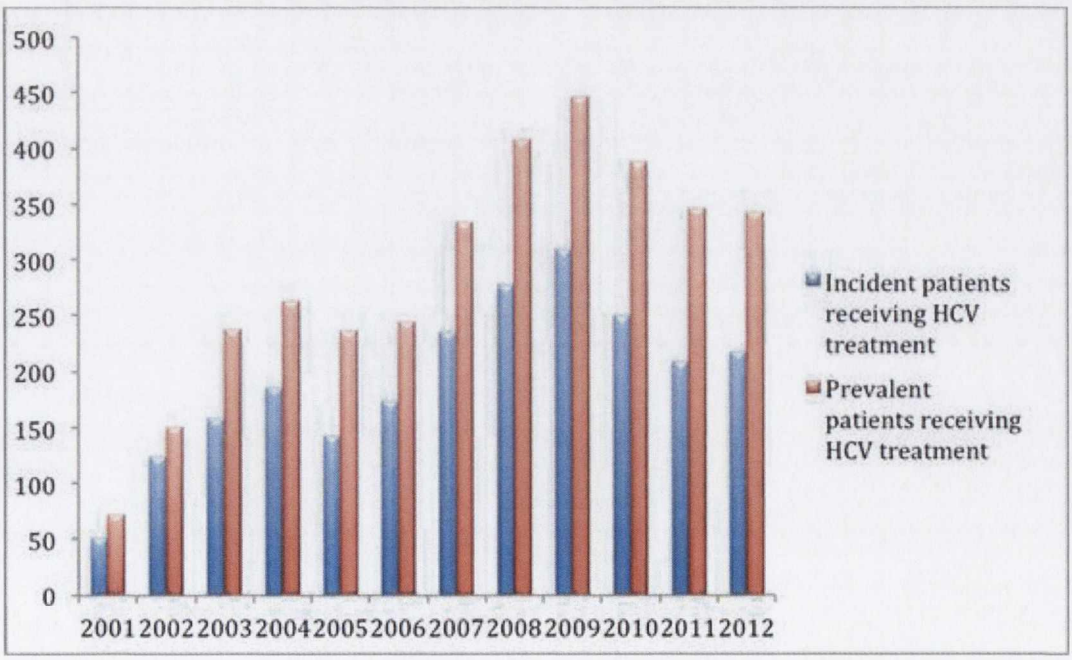



**Figure 4-1 Annual number of Incident and Prevalent Patients receiving treatment for Chronic Hepatitis C**

In total, €27,614,326 was spent on medication for the treatment of HCV from 2001 to 2012. Annual overall drug costs are presented in Figure 4-2. This comprised of antiviral costs of €25,550,270 (€15,460,488 for pegylated interferon and €10,089,781 for ribavirin) and €2,064,056 for haematological growth factor support (€1,406,381 for EPO and €657,675 for G-CSF). Figure 4-3 displays the annual cost of the antivirals and haematological growth factor prescriptions.

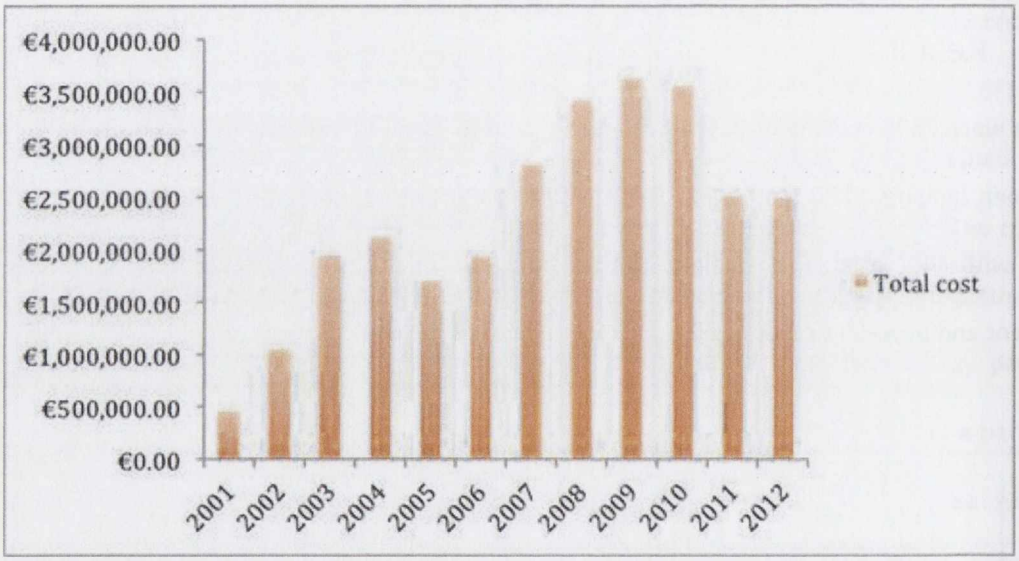



**Figure 4-2 Annual drug cost of HCV treatment including cost of antivirals and haematological growth factors**

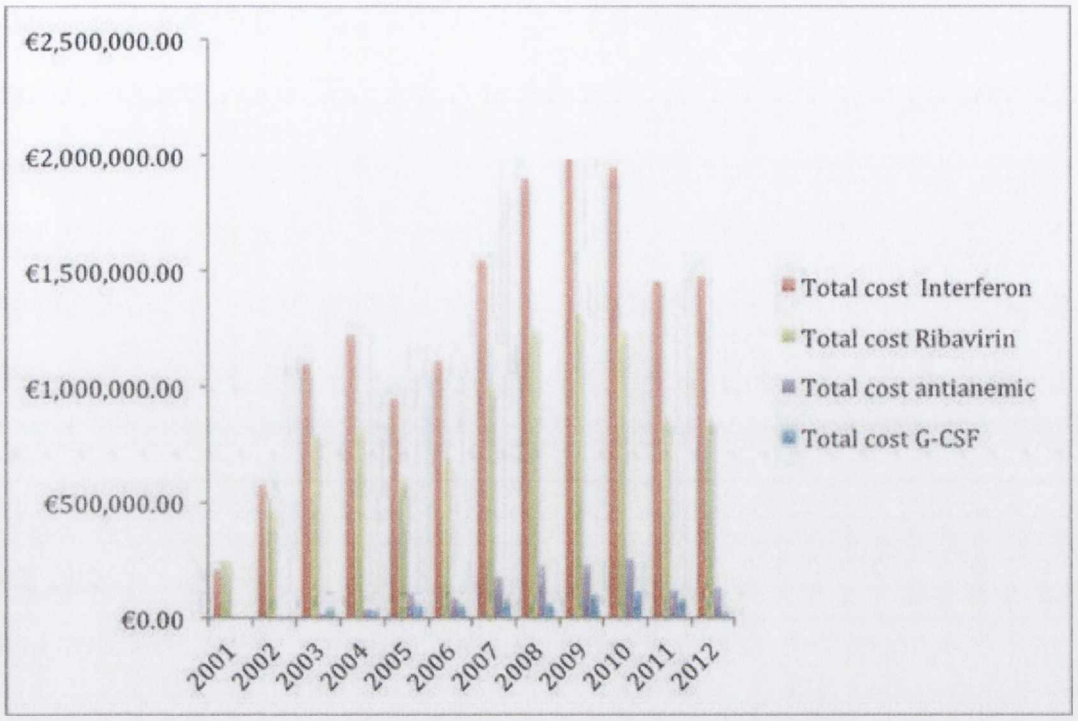



**Figure 4-3 Annual drug cost of individual components of HCV treatment**

The prescription of EPO and G-CSF in this setting peaked in 2007 with 17% of patients initiated on EPO (n=40/235) and 13% initiated on G-CSF (n=31/235). (*Figure 4-4)*

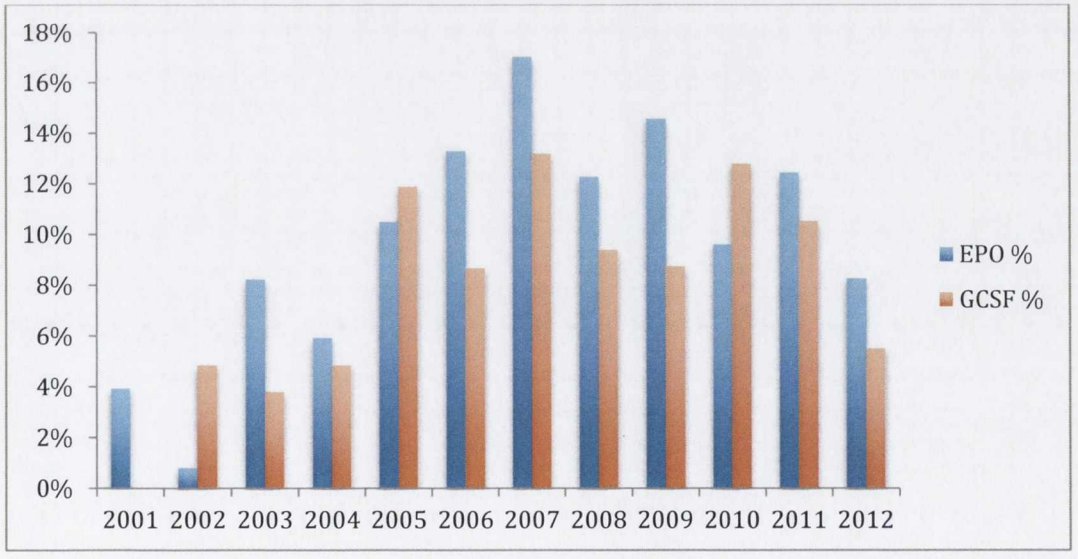



**Figure 4-4 Percentage of incident prescriptions for haematological growth factor support in the setting of HCV treatment**

The average cost per patient initiated on treatment for HCV was €11,771 (95% CI €11,376 – €12,166). The average cost of antivirals per course of HCV treatment was €10,845 (95% CI €10,503-€11,187) and for haematological growth factor support, in those who received such therapy, €4,377 (95% CI €3,908 -€4,598). 10.8% of patients received treatment with EPO (n=252). The average treatment cost per course was €4728 (95% CI €4149-€5307). For those who received treatment with G-CSF (n=203), the average treatment cost per patient was €2,261 (95% CI €2,277 - €3,045).

**Demographics**

Of the 2182 patients captured by the PCRS analysis, 1447 (66%) were male. In 2010, 239 patients were treated, the majority of whom were aged between 25 and 44 years (64%) with the 35-44 years age-bracket most frequent (34%). *(Figure 4-5)*

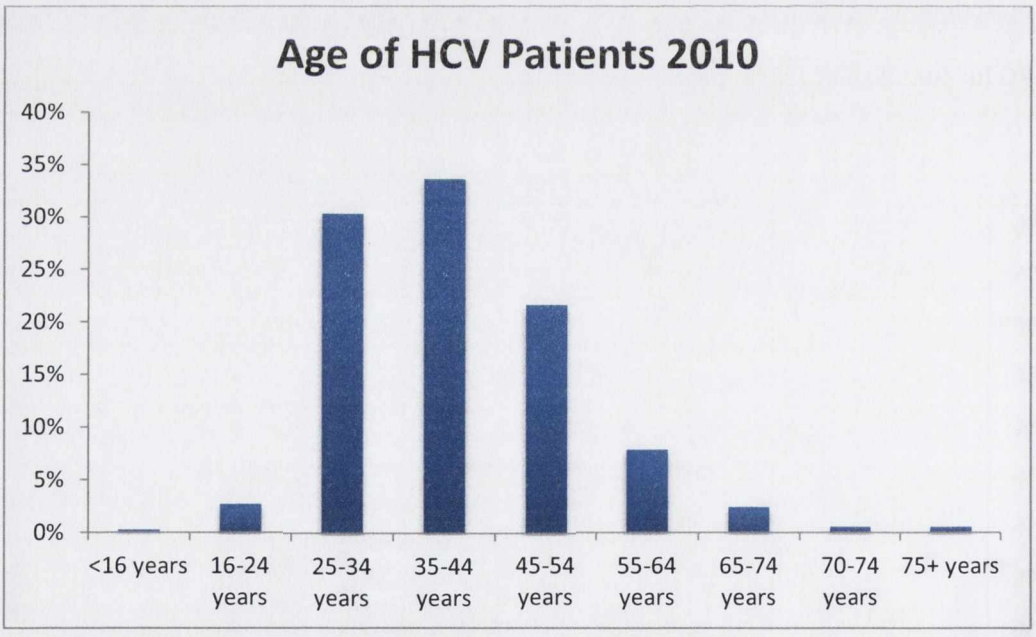



**Figure 4-5 Age of HCV patients treated through the PCRS in 2010**

## 4.4 Discussion

The morbidity and mortality associated with HCV infection, along with the global burden of disease, makes HCV treatment a worldwide priority (8). From the data presented above, treatment with pegylated interferon and ribavirin costs on average €11,000 per patient. There is little doubt that the benefits of HCV treatment to the individual are considerable, with research demonstrating an improvement in health-related quality of life values in Irish patients achieving a sustained virological response or "cure" *(Chapter 6)* (137). From the perspective of the health-care payer, it is possible that investing in HCV treatment at the present time may be cost-effective as it may lead to an avoidance of high-cost health states such as liver transplantation in the future. This has been demonstrated for first and second generation direct-acting antivirals in other healthcare settings (138-140). Chapter 8 will present the findings of the cost-effectiveness analysis of HCV treatment in Ireland.

The budget impact of HCV treatment from 2001-2012 has been significant in Ireland. Twenty-seven million euro has been spent on providing drug treatment for this indication. Two million euro of this budget was provided for haematological growth factor support. The study protocols in the Phase 3 trials of telaprevir did not allow the use of synthetic erythropoietin (141, 142). However, in the Phase 3 trials of boceprevir up to 80% of patients developing anaemia received synthetic erythropoietin (94, 97). Rates of erythropoietin prescribing in clinical practice in Ireland in 2006 and 2007 approached this level. Guidance from the National Institute for Health and Care Excellence (NICE) on the introduction of boceprevir and telaprevir into clinical care, suggests that the use of anti-anaemics in the setting of HCV treatment is relatively rare and the costs associated with them should not be considered (143, 144). While this may be true in the UK health-care setting, we feel that it does not represent current clinical practice in Ireland. Therefore, costs associated with erythropoietin prescription in the setting of HCV treatment will be considered in the economic model in Chapter 8. Once novel interferon-free regimens are available it is possible that they will remove the need for G-CSF

and those that are also ribavirin-free would remove the requirement for EPO support, as anaemia is not a significant adverse effect of the second-generation direct-acting antivirals (3-6). Thus, the money that is currently being spent on the management of haematological adverse effects, could in the future be redirected to the budget for anti-virals and provide a modest cost-offset.

Hepatitis C treatment with pegylated-interferon and ribavirin is lengthy and very resource intensive. Patients experience a myriad of side-effects, both physical and psychological (10). Because of this, they require a large amount of support and monitoring to enable them to complete their treatment regimens successfully. This limits the number of patients that an individual treatment centre can manage. The number of patients treated to date has been relatively modest, (in the order of 5-12% of affected patients), in part because of these capacity constraints. When developing budget impact estimates for the new direct-acting anti-virals, it is important to inform them with estimates of current service capacity. This data provides those figures. However, it is likely that a switch to all-oral regimens of shorter duration and reduced side-effects will result in an increase in capacity.

The role of treatment protocols and strong governance must be emphasised to ensure the appropriate and cost-effective use of these agents. Prospective outcome registries facilitate collection of data on prescriptions that can be linked with patient outcomes such as sustained viral response. The creation of the ICORN National Outcomes Treatment Registry is an important development in this regard and will provide real-world effectiveness data on the new agents as well as information on adverse effects and real-world cost of care.

### 4.4.1 Limitations

There are some limitations with this data. The PCRS data is sourced from pharmacist reports which may underestimate usage as pharmacists receive a flat fee per month regardless of the number of drugs dispensed and will sometimes only report the first drug dispensed. Due to this, it is likely that we have underestimated the total activity and costs of HCV therapy in

Ireland. However, the inclusion of the data from the GUIDE department in St. James Hospital has been an important addition in improving the data capture and the robustness of the estimates. Ideally, the data on prescription and cost would be linked to clinical outcome data to give a more complete picture of the cost-effectiveness of HCV treatment. Unfortunately, this is not possible with the current PCRS database, as it does not include clinical data. The ICORN treatment registry will overcome these limitations in the future. While acknowledging these shortcomings in our data, we feel that it is useful to present an impression of the national activity and costs of HCV treatment over the past decade or so, and to provide an indication of the capacity of the HCV services in Ireland.

## 4.5 Conclusion

The budget impact of HCV treatment has been significant to the Irish healthcare system from 2001-2012. The costs associated with synthetic haematological growth factor support have been important and are likely to remain important with the addition of the first generation protease inhibitors to the treatment paradigms. Therefore, these costs should be considered in an Irish model of the cost-effectiveness of HCV treatment. Chapter 8 will present the results of the cost-effectiveness analysis which will be informed by the data provided in this study.

# Chapter 5

# 5 Hepatitis C in the Era of Direct-Acting Antivirals: Real-World Costs of Untreated Chronic Hepatitis C

## 5.1 Introduction

The cost of caring for patients with HCV infection in Ireland has not been previously established. Care is predominantly provided in an ambulatory care setting and the chronicity of the disease means that ongoing surveillance is required over many years. There are a number of procedures such as liver biopsies and upper GI endoscopy which may be indicated to stage or identify complications of liver disease and imaging such as ultrasound is frequently employed (145).

With increasing fibrosis, the level of health-care utilisation increases substantially. Inpatient care is frequently required for episodes of decompensated cirrhosis and mortality rates increase significantly (146). HCC diagnosis requires complex multi-disciplinary care both on an out-patient and inpatient basis. Strategies such as trans-arterial chemo-embolisation (TACE) and radio-frequency ablation are undertaken, with small proportions referred on for transplantation or chemotherapy with sorafenib (38).

Liver transplantation can be life-saving in patients with decompensated cirrhosis and/or HCC. It is extremely resource-intense both in the short and long-term with significant associated costs and morbidity. Patients require long term follow-up because of the administration of immuno-suppressants and the possiblility of graft failure. Recurrence of HCV in the transplanted organ is universal and progresses rapidly to fibrosis and cirrhosis (34, 35).

With the new developments in HCV therapy, this research project was undertaken to estimate the direct medical costs of HCV care in Ireland, as they were largely unknown. The costs developed were used as inputs for the cost-utility model of novel HCV agents in Ireland presented in Chapter 8.

## 5.2 Methods

### 5.2.1 Micro-costing of Ambulatory Care

The majority of care provided for patients with HCV is ambulatory in nature. A micro-costing project was undertaken at two large tertiary referral Hepatology services in Ireland to establish the cost of an outpatient HCV review. Between them, these units provide clinical care to over 4000 HCV-infected patients. This is approximately half the patients with HCV in Ireland that are currently engaged in HCV care and therefore the costs associated with their care are likely to be representative of HCV care in Ireland (2). In order to establish the staff utilisation involved in providing an outpatient review, the time spent by clerical, nursing, medical and phlebotomy staff in providing a review for a HCV patient was measured. The unit cost associated with this time was calculated using the mid-point of the Health Service Executive (HSE) salary scales for new-entrants in 2010 and adjusted for non-pay salary cost as per guidelines (147-149). In order to establish the laboratory and radiological investigations ordered as part of ambulatory follow-up, the hospital electronic record of 39 patients with chronic HCV infection engaged in routine follow up (e.g. not undergoing HCV treatment) and 28 patients who commenced HCV treatment in 2009 and achieved a sustained virological response (SVR), was interrogated to establish the laboratory investigations ordered for three years between 2011 and 2013. The unit costs applied to these investigations were obtained from laboratory and radiology costs supplied by the finance departments at the participating hospitals and the National Viral Reference Laboratory at University College Dublin. The costs of these investigations were divided by the number of outpatient reviews attended by the patient to derive a mean cost of investigations per visit. The mean costs derived for staff and laboratory utilisation were combined to develop an overall cost for a HCV outpatient review.

In order to establish the number of clinical reviews accessed by patients with HCV, a cohort of 250 patients with HCV attending the two units was identified and stratified into health-states according to clinical, radiological and histological criteria. These are consistent with the natural history of HCV. The health-states established were: mild, moderate, compensated cirrhosis, liver transplantation Year 1, liver transplantation after Year 1, decompensated cirrhosis, hepatocellular carcinoma and sustained virological response (SVR). The hospital electronic patient records of the two units were interrogated to establish how many reviews by medical and nursing staff each patient accessed from 2006 to 2012 and this was multiplied by the cost of review established during the micro-costing project. The SVR patients were assessed for the reviews they accessed post treatment from 2011 to 2013 inclusive. This produced an annual cost of ambulatory care for patients with differing levels of HCV disease severity.

### 5.2.2 Number and Cost of Inpatient episodes for End-stage Liver Disease

In addition to the ambulatory care costs, patients with more severe forms of liver disease such as decompensated cirrhosis, hepatocellular carcinoma and liver transplantation have significant inpatient costs associated with their care. A cohort of patients with decompensated cirrhosis and hepatocellular carcinoma was identified from the prospectively collected clinical database of the Hepatology service of Institution 1. The number of inpatient and outpatient clinical episodes for the last three years of follow up or from diagnosis to death was established through interrogation of the EPR. The HSE Diagnostic Related Group (DRG) costs of an inpatient admission with liver disease from 2011 was applied to the inpatient stays with outpatient costs applied as per the micro-costing study (150). In addition, the duration of prescriptions in months of high-cost drugs such as sorafenib and the frequency of high-cost procedures such as TACE were established and included in the cost estimates for HCC patients. The cost of liver transplantation in the first year post-transplantation was established by combining the cost of the pre-transplant workup with the DRG cost of the liver transplantation

procedure and the number of outpatient and inpatient episodes accessed by patients in the first 12 months post-transplantation. The cost of the pre-transplantation work-up was determined by micro-costing the pre-transplantation work-up protocol of Institution 2 (Appendix 1). This is the sole institution delivering liver transplantation services in the Republic of Ireland. The number of outpatient reviews required by patients in the immediate year post-transplantation and the years thereafter was established from the electronic patient record of Institution 2 and the outpatient cost established from the micro-costing study was applied. The prescription of immunosuppressive therapies post-transplantation was established from the prospectively collected transplantation database in Institution 2 and the costs of these prescriptions was calculated using standard unit costs from the High-tech drug scheme in Ireland, adjusted as per guidelines from the National Centre for Pharmacoeconomics in Ireland (115). The rate of valganciclovir prescription for post-transplantation prophylaxis was estimated at 0.21 based on the rate of cytomegalovirus seroprevalence in a cohort of Irish pregnant women (151). All costs had annual inflation of 4% applied as per guidance from the Irish Department of Finance (109). Table 5-1 summarises the health resources evaluated and included in each health-state.

**Table 5-1 Health resource utilisation considered in derivation of cost of HCV Health-states.**

| Input | Mild | Mod | Comp. Cirrhosis | Decomp. Cirrhosis | HCC | OLT Year 1 | OLT> Year 1 | SVR | Source |
|---|---|---|---|---|---|---|---|---|---|
| **OPD bundle*** *FBC* *Renal profile* *Liver profile* *Coagulation screen* *AFP* *HCV Viral load* *Liver US* *Staff Costs* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Institution costs HSE salary scale 2010 |
| **Liver Biopsy** | ✓ | ✓ | ✓ | × | × | × | × | × | HSE DRG 2011 |
| **OGD§** | × | × | ✓ | ✓ | ✓ | × | × | × | HSE DRG 2011 |
| **Hepatology Medical review** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Micro-costing |
| **Hepatology Nursing review** | ✓ | ✓ | ✓ | ✓ | ✓ | × | × | × | Micro-costing |
| **Inpatient Admission** | × | × | ✓ | ✓ | ✓ | ✓ | ✓ | × | HSE DRG 2011 |
| **Sorafenib** | × | × | × | × | ✓ | × | × | × | HSE PCRS 2014 |
| **TACE¶** | × | × | × | × | ✓ | × | × | × | Institution cost |
| **Oncology/ Palliative OPD** | × | × | × | × | ✓ | × | × | × | HSE DRG 2011 |
| **Dermatology OPD** | × | × | × | × | × | ✓ | ✓ | × | HSE DRG 2011 |
| **Hepatology Dayward review** | × | × | × | × | × | ✓ | ✓ | × | HSE DRG 2011 |
| **Pre-transplant workup** | × | × | × | × | × | ✓ | × | × | Appendix |
| **3months Prophylaxis** | × | × | × | × | × | ✓ | × | × | HSE PCRS 2013 |
| **Immunosuppression** | × | × | × | × | × | ✓ | ✓ | × | HSE PCRS 2013 |
| **Diuretic/Beta-blocker** | × | × | ✓ | ✓ | × | × | × | × | HSE PCRS 2013 |

*Mod = moderate; Comp. cirrhosis = Compensated cirrhosis; Decomp. Cirrhosis = decompensated cirrhosis; HCC = hepatocellular carcinoma; OLT Year 1 = First 12 months of liver transplantation; OLT > Year 1 = Transplantation After First 12 months; SVR = Sustained Viral Response; HSE =Health Service Executive; DRG = Diagnostic Related Group; PCRS = Patient Care Reimbursement Service; OPD = outpatient; *Bundle: FBC = Full Blood Count; Renal Profile = Urea, Creatinine, Sodium, Potassium, Bicarbonate; Liver Profile = Albumin, Alanine aminotransaminase, Aspartate aminotransaminase, Gamma glutamyl transferase, Bilirubin, Lactate Dehydrogenase; Coagulation Screen = Prothrombin Time, Activated partial thromboplastin time, International Normalised Ratio; AFP = Alpha fetoprotein; § OGD = Oesophago-gastro-duodenoscopy; ¶ TACE= Transarterial chemoembolisation;*

### 5.2.3 Statistical Analysis

Descriptive statistics were performed on the results from the micro-costing project to give average values with 95% Confidence Intervals (CI). Mean time required for clinical review was examined for significant differences depending on provider and clinical indication using an independent t-test for those elements with two categories and a one-way ANOVA for those with greater than 2 categories. A p-value of less than 0.05 was considered significant. SPSS V21 was used for this analysis.

Given the positive skew of the annual cost estimates for the health-states, non-parametric bootstrapping was performed to establish valid means(152). Mean and 95% Confidence intervals (95% CI) values are presented. The analysis was performed using Microsoft Excel.

This study received approval from the Ethics Committees of all participating institutions.

## 5.3 Results

### 5.3.1 Micro-costing of Ambulatory care

Ninety medical reviews of HCV patients were identified and timed. The average time spent per medical review was 17 minutes. (95% CI 15, 19). Mean review times in both clinical sites were the same. There was a significant difference in the time required for a clinical review undertaken by a consultant compared to one performed by a registrar (mean time 13 versus 19 minutes p=0.001) and in the time required to review a patient depending on their indication for review, as those with chronic HCV required more time. Patient attending for a first review required an average of 16 minutes (95% CI 13,19), those for routine HCV monitoring required an average of 18 minutes (95% CI 16, 20), while those attending for review post-sustained viral response required on average 8 minutes (95%CI 6,9) p=0.03.

Thirty clinical nurse specialist reviews of patients undergoing or being assessed for HCV treatment were timed. The average time spent was 27 minutes (95%CI 22, 33). There was a significant difference in the average time required for review depending on clinical indication.

Those for pre-treatment assessment or work-up required a mean of 20 minutes (95%CI 13, 28), those reviewed during dual therapy with pegylated interferon and ribavirin required a mean of 27 minutes (95% CI 15, 39), while those being reviewed on triple therapy with pegylated interferon, ribavirin and a HCV protease inhibitor required a mean time of 36 minutes (95% CI 28, 44) p=0.04.

Eighty-one HCV positive patients had a blood draw that was timed during their clinic review. The average time required by phlebotomy staff for a blood draw was 3.6 minutes (95%CI 3.0, 4.2). There was no difference in average times between sites. Sixty-eight HCV patients had the administrative time required for their outpatient review assessed. The average time taken by administrative staff to check patients into and out of the outpatient clinic was 2.1 minutes (95%CI 1.8, 2.4). There was no difference in the time required between the 2 sites. An additional 14 minutes of administrative time per patient was included to account for the time required to source the patient medical records (4 minutes) and type the letter (10 minutes) to the patients' general practitioner.

The overall cost of an outpatient HCV medical review including staff utilisation *(medical, administration, phlebotomy services)* (€41) and laboratory/radiology tests (€95) was estimated to be €136 (€3.60 SD).

The overall cost of a HCV clinical nurse specialist review including staff utilisation *(nursing, administration, phlebotomy services)* (€33) and laboratory/radiology investigations (€95) was estimated to be €128 (€7.30 SD).

### 5.3.2 Annual Healthcare resource utilisation of patients with HCV

Two hundred and twenty-five patients were identified and categorised by their degree of liver disease, representing 819 patient-years of follow-up. One hundred and sixty-four (73%) were male and the mean age of the cohort was 46 years. Table 2 presents a summary of the demographics and healthcare resource utilisation of these patients established through interrogation of the EPR.

**Table 5-2 Summary of Patient Demographic and Healthcare Utilisation characteristics in differing HCV Health-states**

| Characteristic | Mild | Mod. | Comp. Cirrhosis | Decomp. Cirrhosis | HCC | Transplant Year 1 | Transplant > Year 1 | SVR |
|---|---|---|---|---|---|---|---|---|
| **N** | 40 | 29 | 24 | 13 | 27 | 33 | 31 | 28 |
| **Mean Age (SD)** | 38 (8) | 48 (10) | 45 (9) | 46 (7) | 55 (11) | 47 (9) | 54 (9) | 34 (10) |
| **Male n (%)** | 25 (61) | 16 (55) | 25 (89) | 12 (98) | 23 (85) | 22 (67) | 19 (66) | 22 (79) |
| **Patient years of follow-up** | 214 | 137 | 102 | 23 | 39 | 33 | 187 | 84 |
| **Annual mean number of medical reviews (95%CI)** | 1.3 (1.1, 1.5) | 1.4 (1.2,1.7) | 1.8 (1.5, 2.1) | 4.6 (4.2, 4.9) | 5.2 (4.6, 5.8) | 11.9 (10.4, 13.2) | 4.3 (4.0, 4.6) | 0.36 (0.22, 0.5) |
| **Annual mean number of nursing reviews (95% CI)** | 0.5 (0.3, 0.7) | 0.9 (0.6, 1.2) | 1.8 (0.9, 2.6) | 5.1 (4.3,5.9) | 3.6 (3.1, 4.1) | n/a | n/a | 0.1 (0.0, 0.04) |
| **Annual mean number of inpatient episodes (95%CI)** | n/a | n/a | 0.2 (0.06, 0.4) | 2.5 (2.1, 3.0) | 2.1 (1.8, 2.3) | 1.1 (0.6, 1.6) | 0.24 (0.1, 0.38) | n/a |

*Mod = moderate; Comp. cirrhosis = Compensated cirrhosis; Decomp. Cirrhosis = decompensated cirrhosis; HCC = hepatocellular carcinoma; Transplant Year 1 = First 12 months of liver transplantation; Transplantation > Year 1 = Transplantation after First 12 months; SVR = Sustained Viral Response*

Seventeen percent of the evaluated cohort had mild disease (n=40). They accessed an average of 1.5 ambulatory care visits per year. Seventy percent (n=28) had undergone a liver biopsy. Twenty-nine patients (13%) had moderate disease and an average of 2.5 ambulatory care episodes per annum. Eighteen patients (62%) had had a liver biopsy. Twenty-four patients (11%) had compensated cirrhosis, of whom fourteen had had a liver biopsy performed (58%) and sixteen had had upper GI endoscopy (67%). Nine patients with compensated cirrhosis required a liver-related inpatient hospital stay (38%) and one patient was admitted to the intensive care unit on four occasions.

Six percent of the evaluated cohort (n=13) had decompensated cirrhosis. Eleven (85%) required inpatient admissions. Four patients died over the course of the follow-up (31%). Three patients (23%) required an Intensive care unit admission. Eleven patients (85%) underwent upper GI endoscopy; the majority (n=7) had one procedure (range 0-2).

Twelve percent of the cohort (n=27) had HCC. Twenty-two patients (81%) required inpatient admissions. Six patients (22%) received treatment with sorafenib for an average duration of four months (95%CI 3.1, 5.5). Eighteen (67%) had a TACE procedure carried out. The majority had this performed once (n=10) however one patient had 6 procedures (95% CI 0.98, 1.4). Sixteen patients died over the course of the follow-up (59%) consistent with the high mortality seen with this condition.

Ten percent of the cohort (n=28) had been treated successfully for HCV. The cost of their follow-up care was evaluated. Their retention in ongoing clinical care was less than expected, with 46% (n=13) not accessing HCV review in the 3 years post-SVR. Five patients (18%) had cirrhosis. The mean number of annual medical reviews was 0.36 (95CI 0.2, 0.5). If only the patients who had attended (n=15) were considered in the cost estimate, the annual mean cost was €83 (95% CI €66, €101).

### 5.3.3 Healthcare resource utilisation of patients receiving Liver Transplantation

The cost associated with the pre-transplant workup including staff costs, laboratory and radiological investigations was €2828. The inputs considered as part of the pre-transplant work-up are displayed in Appendix 1. The DRG cost of the liver transplantation procedure in 2011 was €124,425. The mean number of outpatient reviews in the first year post-transplant was 12 (95%CI 10.4, 13.2) and four (95%CI 4.0, 4.6) in the years thereafter. The cost of an ambulatory care review including monitoring of immunosuppression was €184.54 (€3.60 SD) Sixteen patients (48%) required re-admission under the liver service in the first year post-transplant. The mean number of admissions was one (95%CI 0.6, 1.6). Fifteen (48%) patients required an inpatient stay under the liver service in the years following their first year post-transplant. Prednisolone was the most commonly prescribed immunosuppressive in the first year post-transplant (88%), followed by tacrolimus (81%) and mycophenolate mofetil (75%). In subsequent years the rate of prednisolone prescribing fell (33%) and tacrolimus was the most commonly prescribed immunosuppressant (66%). The cost of immunosuppressive drugs was €3,713 per person in the first year and €3,667 per person per year thereafter. The cost of antimicrobial prophylaxis was €1081 in the first year post-transplantation based on three months therapy with co-trimoxazole and either valaciclovir (79%) or valganciclovir (21%).

### 5.3.4 Direct Medical Cost of HCV care in Ireland

The direct medical costs of HCV care rose substantially with progression of liver disease (Figure 5-1). Patients with mild liver disease accrued the least costs (€398) with patients in the first year post-transplantation accruing the most cost (€137,176). Patients with non-cirrhotic disease had significantly less cost than those with end-stage liver disease (ESLD). Table 5-3 summarises the mean cost and 95% confidence intervals of the different HCV health-states.

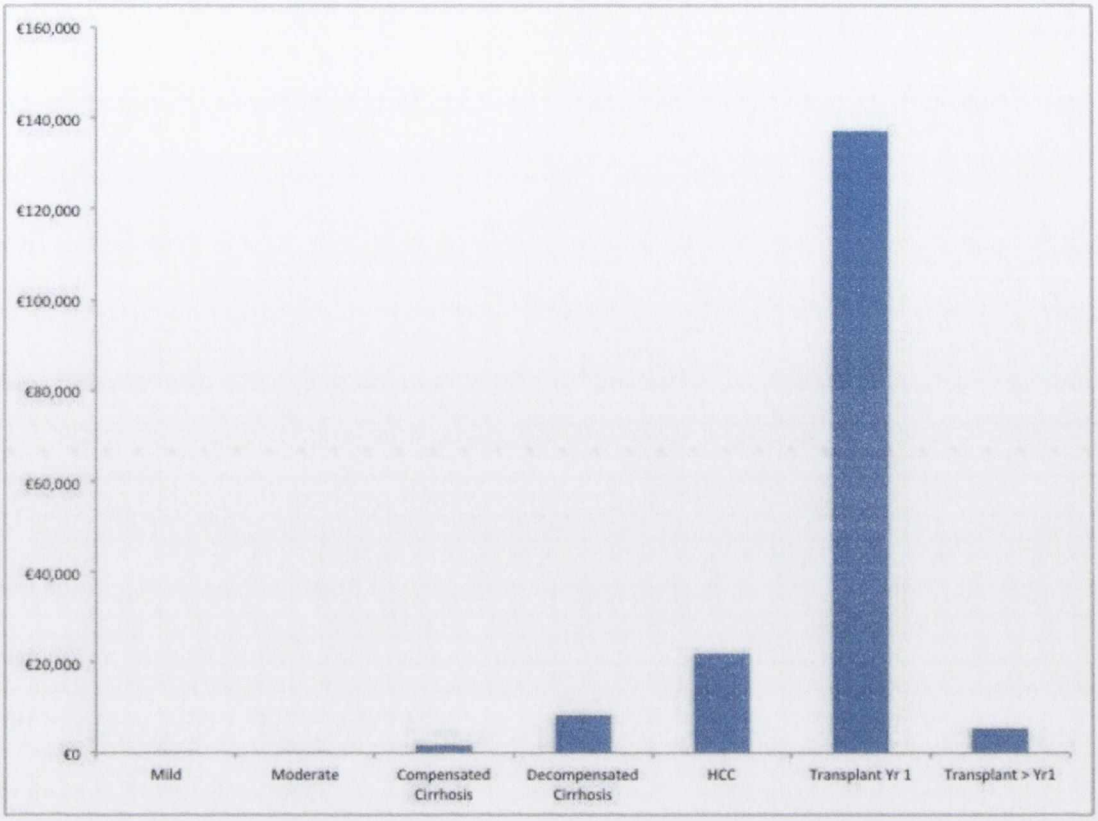



**Figure 5-1 Annual Direct Medical Cost of HCV care for Different HCV Health-states**

**Table 5-3 Annual Mean Direct medical costs of chronic HCV care for patient with different stages of liver disease in Ireland**

| HCV Health-state | Mean Annual Cost | (95% CI) |
|---|---|---|
| Mild | €398 | (€336, €482) |
| Moderate | €417 | (€335, €503) |
| Compensated cirrhosis | €1,790 | (€990, €3164) |
| Decompensated cirrhosis | €8,303 | (€3,945, €14,637) |
| Hepatocellular carcinoma | €21,992 | (€15,222, €29,467) |
| Transplant Year 1 | €137,176 | (€136,024, €138,306) |
| Transplant after Year 1 | €5,337 | (€4942, €5799) |
| Sustained Virological Response | €83 | (€66, €102) |

## 5.4 Discussion

The scale of the HCV epidemic and the rapidly expanding formulary of novel therapies undergoing regulatory assessment and re-imbursement decisions worldwide, mean that this disease area is of great interest in many healthcare systems (8, 153-156). Treatment of HCV with pegylated interferon (Peg-IFN) and ribavirin (RBV) has previously been shown to be cost–effective in settings other than Ireland, as has triple therapy with Peg-IFN, RBV and a NS3/4A protease inhibitor (138, 157). However, uptake of these therapies was low due to their relatively limited effectiveness, long and complex regimens and substantial side-effects (11). This resulted in a contained budget impact for payers although little advance from the perspective of patients with HCV. Future treatment options offer the possibility of all-oral treatment regimens with good tolerability and excellent efficacy (3, 4, 6, 158). As many of the previous barriers to HCV treatment have been comprehensively addressed, cost of treatment will become one of the most significant. Treatment costs may be offset by the reduction in the cost of chronic care elicited by successful treatment. However, real-world cost data for chronic HCV care is sparse internationally and not previously available in Ireland (153, 159-161). Submissions to health-technology assessment agencies have been hampered by the lack of availability of good-quality, up-to-date cost estimates in this disease area with many of them utilising costs published in 2006 and established in 2003 (131, 160). These are likely to be underestimates, particularly in the high-cost areas of hepatocellular carcinoma and liver transplantation, as treatment options such as sorafenib and TACE were not available in 2003 and prescribing practices in post-transplant immunosuppression have also changed (162). This study demonstrates that the direct medical cost associated with HCV care in Ireland is substantial and that with progression of liver disease the costs associated with care increase exponentially. This is consistent with recent reports from managed care insurance databases in the US, where the cost of HCV care increased substantially with the development of cirrhotic liver disease (153, 159, 163). It is estimated that while the incidence of HCV is falling in many

healthcare systems, the peak consumption of healthcare resources is yet to come as increasing numbers of patients with HCV develop complications of their chronic viral hepatitis (77, 153). The cost of providing care to HCV patients will continue to rise unless treatment interventions are initiated to avert disease progression and avoid high-cost health-states. Given the large proportion of patients who are currently undiagnosed, treatment strategies aimed at future healthcare cost-containment will only be successful if patients are identified prior to their presentation with complications of end-stage liver disease. The importance of screening as part of this paradigm has been highlighted by recent international recommendations (164, 165). The follow-up costs of patients who had achieved an SVR in this cohort were low in comparison to patients with ongoing chronic infection and significantly lower than those for patients with end-stage liver disease.

While the costs associated with advanced liver disease in HCV are substantial, the vast majority of patients with HCV at present have mild or moderate disease (69, 159). The bulk of their management occurs through ambulatory care and therefore it is appropriate to develop accurate real-world unit costs of outpatient visits in this setting. Micro-costing is the recommended method of establishing unit costs although in practice it is rarely done due to time constraints (116, 166). To our knowledge, this study presents the most detailed breakdown of a HCV routine outpatient visit. The detail provided will allow others to derive costs by applying unit costs reflective of their own practice to the resource utilisation of healthcare personnel and investigations presented. It provides a "bottom-up" perspective to HCV care that is lacking from cost estimates derived from large healthcare insurance databases and comprehensively establishes ambulatory, inpatient and pharmacy direct cost estimates for all disease stages of HCV.

### 5.4.1 Limitations

This study does not consider costs associated with HCV treatment. The cost of HCV treatment in Ireland will be established through the prospectively collected HCV treatment registry established under the auspices of the Irish HCV Outcomes and Research Network (ICORN). This will provide real-world cost estimates of HCV therapy to inform cost-effectiveness and budget impact analysis in the future. Societal costs are not considered in this study as it concentrates on direct medical costs from the perspective of the payer. As histological criteria were used as part of the definition to establish the health-states that patients were placed in, a relatively large proportion of the cohort had received a liver biopsy. This may not reflect future practice with the increasing availability of transient elastometry. The majority of HCV care in Ireland is provided by the publicly funded health care system and therefore these cost estimates may not reflect costs in healthcare systems with multiple payers. The SVR costs included patients with cirrhosis however there was limited attendance of these patients over the follow up period of 3 years. It would be expected that patients with cirrhosis would require follow up and investigation despite having achieved an SVR, owing to their underlying liver disease. Therefore, the cost of SVR established may not fully reflect the cost of managing cirrhotic patients after successful treatment.

## 5.5 Conclusion

Cost-utility analysis is important to establish the true value and opportunity cost associated with HCV treatment in Ireland. The detailed micro-costing estimates above, which consider ambulatory, inpatient and pharmacy real-world costs in Ireland, will be used to inform the cost-utility model presented in Chapter 8. This input data was not available prior to the conducting of this study and as such represents valuable progress in the establishment of an economic knowledge base around HCV care in Ireland.

# Chapter 6

# 6 Health-State Utilities in Patients with Different Stages of Hepatitis C Infection

## 6.1 Introduction

Cost-effectiveness models combine evidence on efficacy, health related quality of life and costs to calculate whether a technology represents value for money. Health-related quality of life (HRQOL) in cost-effectiveness models is represented by society-derived preferences for health-states. These values are termed "utilities" and can be measured directly (using methods such as time-trade-off or standard gamble) or indirectly (using tools such as the EQ-5D) (167). While there is extensive literature on quality of life in hepatitis C, health-state utility data is relatively sparse and there are no values available in an Irish HCV-infected population (160, 167-175).

The Euroqol questionnaire is a generic HRQOL tool (118, 119). It is an indirect measurement of health utility which has been shown to correlate well with direct measures of utility in patients with chronic liver disease (167). It is the HRQOL instrument favoured by NICE and one of those (along with the SF-6D) prefered by the NCPE (109, 176). A generic HRQOL tool was chosen to facilitate comparisons with utilities derived from other disease areas. Non-preference based, disease-specific HRQOL tools may have advantages with regards to clinical acceptability, however the results obtained are less generalisable and not based on societal preferences (177). The EQ-5D has been criticised for only having three levels in its responses leading to concern that it was insensitive to small changes in utility scores and to ceiling effects (172). To address these elements, the EQ-5D five level (EQ-5D 5L) was developed to increase reliability and sensitivity while potentially reducing ceiling effects (178, 179). This study was undertaken to derive health-state utilities in Irish patients infected with HCV using the EQ-5D 5L. The

results presented will provide utility data for the cost-effectiveness model presented in Chapter 8.

## 6.2 Methods

### 6.2.1 Patient selection

The study was undertaken between September 2011 and October 2012 in two tertiary care Hepatology units in Dublin, Ireland. The unit in St. James Hospital has a large cohort of HCV patients encompassing the full spectrum of clinical disease, whereas the unit in St. Vincent's University Hospital is the single centre providing liver transplantation services in Ireland and receives nationwide referrals for transplant assessment. As such, it has a higher proportion of patients with more advanced liver disease. The study was approved by the ethics committees of both centres. Consecutive adult patients with documented current or past HCV infection attending the hepatology outpatient services in these units were invited to complete a questionnaire gathering clinical, demographic and HRQOL information. The questionnaire used is presented in Appendix 2. In an effort to be inclusive of all clinical conditions associated with HCV, six inpatients with HCV-related decompensated cirrhosis were also recruited. The questionnaire was completed during a face-to-face interview with the author of this thesis. Medical records and computerised laboratory and radiology results were interrogated for clinical and virological endpoints. Two hundred and seventy three patients were invited to take part with two hundred and seventy (99%) agreeing to complete the questionnaire.

### 6.2.2 Health-Related Quality of Life measurement

The EuroQoL 5-Domain (EQ-5D) self-report questionnaire was used to assess HRQOL and generate utility scores. The EQ-5D is a generic preference-based instrument that consists of two parts. The descriptive system comprises of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each of these dimensions has five levels to choose from: no problems, slight problems, moderate problems, severe problems, extreme

problems. Patients describe the health-state in which they perceive themselves to be across these five dimensions, and then valuations or preferences derived from the general public are applied to these health-states. In the absence of Irish preferences, those derived from the UK population were used (120). The second part of the questionnaire comprises of a visual analogue scale (VAS). This records the individuals self-rated health on a vertical scale where the endpoints are labelled 'Best imaginable health-state (100)' and 'Worst imaginable health-state (0)'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Use of the questionnaire for this study was registered with the EuroQol group (118).

### 6.2.3 Health-States

Patients were assigned to 8 different health-states correlating with typical disease progression in HCV; chronic HCV infection (non-cirrhotic), compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation within 1 year, liver transplantation greater than 1 year previously, sustained virological response after treatment for HCV (SVR), and spontaneous virological clearance without treatment for HCV (SVC) *(Table 6-1)*. Where histological or transient elastography results were available on patients in the chronic HCV infection (non-cirrhotic) group, they were further subdivided into mild, moderate or unknown (non-cirrhotic) *(Table 6-1)*. As there were minimal differences in the utility scores between these groups and they are treated similarly in clinical practice, they were classed together for the majority of the analysis. However, individual results are presented where they are felt to be of relevance.

**Table 6-1 Definitions of HCV Health-States**

| Health-state | Definition |
|---|---|
| Mild | Liver biopsy demonstrating modified ISHAK fibrosis score of 0,1 or 2<br>AND/OR<br>transient elastography score of <8.8 |
| Moderate | Liver biopsy demonstrating modified ISHAK fibrosis score 3 or 4<br>AND/OR<br>Transient elastography score of >8.8 <14.6 |
| Unknown (non-cirrhotic) | No histological or transient elastography score available.<br>No radiological, clinical or biochemical evidence of cirrhosis |
| Chronic Infection (non-cirrhotic) | Combination of "Mild", "Moderate" and "Unknown" |
| Compensated cirrhosis | Liver biopsy demonstrating modified ISHAK fibrosis score of 5 or 6<br>AND/OR<br>radiological evidence of cirrhosis<br>AND<br>without current or previous episodes of<br>ascites/ variceal bleeding/ hepatic encephalopathy/ hepatorenal syndrome |
| Decompensated cirrhosis | Liver biopsy demonstrating modified ISHAK fibrosis score of 5 or 6<br>AND/OR<br>radiological evidence of cirrhosis<br>AND<br>current or previous episodes of<br>ascites/variceal bleeding/encephalopathy/hepatorenal syndrome |
| Transplantation < 1 year | Liver transplant within the previous 12 months |
| Transplantation > 1 year | Liver transplant performed 12 months ago or longer |
| HCC | Hepatocellular carcinoma diagnosed on biopsy or by typical radiological findings |
| Sustained virological response (SVR) | HCV PCR negative 24 weeks or longer after HCV treatment |
| Spontaneous virological clearance (SVC) | HCV PCR negative without prior HCV treatment |

### 6.2.4 Statistical Analysis

Patient demographic and clinical characteristics were analysed using descriptive statistics. Continuous variables are presented as means with standard deviation (SD) and categorical variables as proportions. As the distribution of the utility scores was non-normal, non-parametric tests were used to assess for differences in median utilities between the health-state and demographic subgroups. Mann-Whitney U tests were performed to compare median utility scores in subgroups with two outcomes while the Kruskal-Wallis test was used to compare median utility values for variables with more than two outcomes. The logit distribution of the utility score was examined to assess for a significant effect due to lack of normality, but none was found. Therefore, multivariate, backwards, stepwise linear regression analysis was performed on variables found to have a statistically significant effect on utility scores on univariate analysis. With an $f^2$ of 0.4, 80% power and a significance level of $\alpha$=5%, a sample size of 204 would be required (using pwr.f2.test in R version 2.12). It was planned to recruit 34 participants at each HCV level. Given the differing prevalence of the groups, a larger sample was collected overall. Statistical significance was taken as a p-value of <0.05. The analysis was performed using SPSS version 16®.

## 6.3 Results

### 6.3.1 Demographic and Clinical Characteristics

The mean age of the patients was 45 years. Patients with chronic HCV (non-cirrhotic) were younger than those in the HCC, post-transplant >1 year and SVC groups ($p< 0.001$). The majority (180/270; 66%) were male. Ninety-three percent of the cohort was Caucasian, with six percent Asian, two Africans and one patient from South America. Time since HCV diagnosis was available for two hundred and fifty-three patients (94%). The mean time since diagnosis was twelve years (range 1-27 years). Forty-five percent (n=109) of patients had not completed second-level education, with eleven percent (n=29) only having primary school education.

Forty-one percent (n=111) were jobseekers or on disability allowance; thirty-eight percent (n=102) were in paid employment. Patients with more severe disease stages such as decompensated cirrhosis, HCC and post-liver transplantation were significantly less likely to be in paid employment (p=0.01) than those with milder disease.

HCV genotypes 1 and 3 were the most commonly encountered. Fifty-five percent of patients had genotype 1 infection (n=150) and 30% percent had genotype 3 (n=81). Forty percent of the study patients were treatment experienced (n=107) of whom thirty-six percent had achieved an SVR (n=38). The mean time since treatment for those with an SVR was five years (range 1-19 years). The most frequently cited acquisition risk factor for HCV was injecting drug use (IDU) (n=155; 57%). Thirty–two percent of the patients had advanced liver disease related to HCV infection (n=87); seventeen percent had cirrhosis (n=46), sixteen percent (n=43) had undergone liver transplantation and eight patients had HCC. The median ALT was 44 IU/ml (range 6-796 IU/ml) and the median HCV viral load was 481,097 IU/ml (range 0-68,467,679 IU/ml). Table 6-2 summarises the demographic and clinical characteristics of the patients in the differing HCV health-states.

**Table 6-2 Demographic and Clinical characteristics of patients in different HCV health-states**

| | Total (n=270) | Chronic Infection (n=140) | Comp. Cirrhosis (n=26) | Decomp. Cirrhosis (n=12) | Transplant (n= 41) | HCC (n=8) | SVR (n=38) | SVC (n=5) |
|---|---|---|---|---|---|---|---|---|
| **Demographics, (n (%))** | | | | | | | | |
| Age ((mean, (SD)) | 45 (11) | 41 (10) | 47 (10) | 48 (8) | 53 (9) | 59 (10) | 43 (12) | 56 (14) |
| Male | 180 (67) | 87 (62) | 23 (88) | 10 (83) | 28 (68) | 5 (63) | 26 (69) | 1 (20) |
| White | 251 (93) | 127 (91) | 26 (100) | 11 (92) | 41 (100) | 6 (75) | 35 (92) | 5 (100) |
| Completed Highschool | 143 (53) | 72 (51) | 11 (42) | 7 (58) | 20 (49) | 4 (50) | 26 (68) | 3 (60) |
| Married/common-law | 113 (41) | 57 (41) | 12 (46) | 4 (33) | 20 (49) | 5 (63) | 13 (34) | 2 (40) |
| | | | | | | | | |
| Paid Employment | 102 (38) | 59 (42) | 10 (38) | 2 (17) | 6 (15) | 2 (25) | 21 (55) | 2 (40) |
| Jobseeker/Disability | 111 (41) | 50 (36) | 10 (38) | 9 (75) | 29 (71) | 4 (50) | 9 (24) | 0 (0) |
| House-duties | 33 (12) | 20 (14) | 4 (15) | 1 (8) | 2 (5) | 1 (13) | 3 (8) | 2 (40) |
| Retiree | 14 (5) | 4 (3) | 1 (4) | 0 (0) | 3 (7) | 1 (13) | 4 (11) | 1 (20) |
| Other | 10 (4) | 7 (5) | 1 (4) | 0 (0) | 1 (2) | 0 (0) | 1 (3) | 0 (0) |
| **Clinical (n, (%))** | | | | | | | | |
| Years since HCV dx (mean (SD)) | 12 (7) | 11(7) | 12 (7) | 15 (5) | 14 (6) | 7 (5) | 11 (6) | 15 (6) |
| ALT, (median (range)) | 44 (790) | 49 (778) | 74 (246) | 55 (198) | 55 (68) | 67 (756) | 18 (56) | 20 (19) |
| Liver Biopsy | 168 (62) | 95 (68) | 19 (73) | 6 (50) | 15 (37) | 4 (50) | 29 (76) | 0 (0) |
| | | | | | | | | |
| **Genotype** | | | | | | | | |
| 1 | 150 (55) | 89 (64) | 10 (38) | 10 (84) | 23 (56) | 2 (25) | 16 (42) | 0 (0) |
| 2 | 9 (3) | 6 (4) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 2 (5) | 0 (0) |
| 3 | 81 (30) | 33 (24) | 14 (54) | 1 (8) | 10 (24) | 4 (50) | 18 (47) | 1 (20) |
| 4 | 6 (2) | 2 (1) | 2 (8) | 0 (0) | 0 (0) | 1 (12.5) | 1 (3) | 0 (0) |
| Unknown | 24 (9) | 10 (7) | 0 (0) | 1 (8) | 7 (17) | 1 (12.5) | 1 (3) | 4 (80) |
| | | | | | | | | |
| **Prior HCV treatment** | 120 (44) | 29 (21) | 10 (38) | 6 (50) | 21 (51) | 3 (38) | 38 (100) | 0 |
| SVR | 38 (32) | n/a | n/a | n/a | n/a | n/a | 38 (100) | n/a |
| Relapse | 19 (16) | 8 (28) | 5 (50) | 1 (17) | 4 (19) | 1 (13) | n/a | n/a |
| Partial responder | 11 (9) | 7 (24) | 1 (10) | 1 (17) | 2 (9) | 0 (0) | n/a | n/a |
| Null responder | 32 (27) | 9 (31) | 3 (30) | 4 (67) | 14 (67) | 2 (25) | n/a | n/a |
| On-treatment | 13 (11) | 9 (31) | 4 (40) | 0 (0) | 0 (0) | 0 (0) | n/a | n/a |
| SVR24 awaited | 5 (4) | 4 (14) | 1 (10) | 0 (0) | 0 (0) | 0 (0) | n/a | n/a |
| Missing | 2 (2) | 1 (3) | 0 (0) | 0 (0) | 1 (5) | 0 (0) | n/a | n/a |
| | | | | | | | | |
| **Acquisition Risk** | | | | | | | | |
| IDU | 157 (58) | 86 (61) | 18 (69) | 9 (75) | 15 | 6 (75) | 22 (58) | 1(20) |
| Blood Products | 47 (17) | 15 (11) | 3 (12) | 3 (25) | 14 | 1 (13) | 8 (21) | 3 (60) |
| Endemic Country | 25 (9) | 20 (14) | 1 (4) | 0 (0) | 0 (0) | 1 (13) | 2 (53) | 1 (20) |
| Sexual | 2 (1) | 2 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Unknown | 39 (14) | 17 (12) | 4 (16) | 0 (0) | 12 | 0 (0) | 6 (16) | 0 (0) |

*Abbreviations: SD = standard deviation; n/a = not applicable; Comp. = Compensated; Decomp. = Decompensated; HCC = hepatocellular carcinoma; SVR = sustained viral response; PCR –ve = spontaneous viral clearance; dx = diagnosis; ALT= alanine transaminase.*

### 6.3.2 Utility scores

Two hundred and sixty eight patients completed the HRQOL portion of the questionnaire (99%). The mean utility score for the cohort was 0.7 (0.24 SD). The mean utility scores for patients with mild disease (n= 70) was 0.76 (0.16 SD), for moderate disease (n=25) was 0.71 (0.21 SD) and for unknown non-cirrhotic (n= 43) was 0.74 (0.19 SD). The mean utility scores and 95% confidence intervals for the health-states are presented in Figure 6-1.

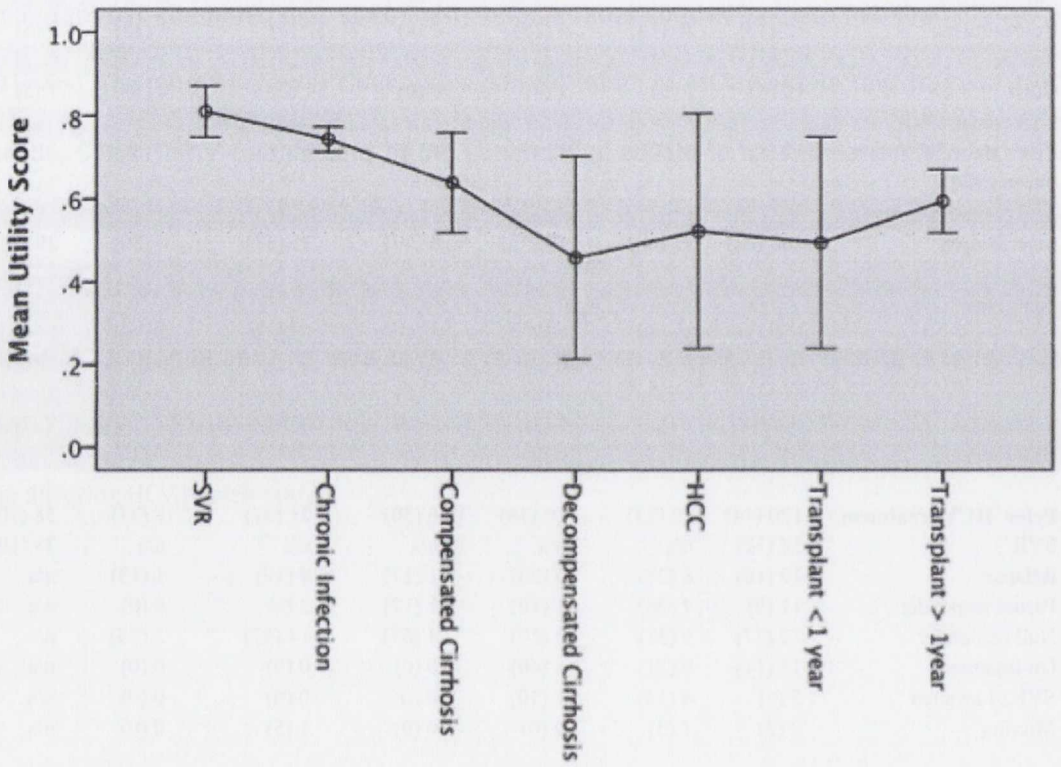



**Figure 6-1 Mean Health-state Utilities for the differing HCV health-states. Error bars indicate 95% Confidence Intervals.**

*Abbreviations: SVR = Sustained Virological Response; HCC = Hepatocellular carcinoma; Transplant < 1 year = Liver transplantation within the past 12 months; Transplant >1 year = Liver transplantation greater than 12 months previously*

*Univariate Regression Analysis*

Patients who had received treatment for HCV had significantly higher utility scores than those that had not been treated (0.74 versus 0.67 p=0.03). Those who had achieved an SVR reported the highest mean health-state utility overall. This was significantly higher than patients who had ongoing viral infection (0.81 versus 0.68, p<0.001). Table 6-3 summarises utility scores for treatment-naïve and treatment-experienced patients with differing levels of HCV-related liver disease.

Patients who had undergone liver transplantation due to HCV reported lower utility scores in the first year post-transplant than in the subsequent years (0.49 versus 0.59 p=0.5), however even in the first year post-transplant they were higher than those reported by patients with decompensated cirrhosis (0.46). Health state utility was not significantly affected by other clinical characteristics such as ALT level, HCV viral load or HCV genotype. Increasing time (in years) since HCV diagnosis was associated with statistically significant lower health-utility scores (-0.008 for each additional year, p=0.001) as was the presence of cirrhosis (p=0.02). Demographic characteristics such as gender (mean utility value: male 0.7; female 0.7), marital status (mean utility value: current relationship 0.7; not currently in relationship 0.7), ethnicity (mean utility value: Caucasian 0.7; Non-caucasian 0.71) and IDU (mean utility value: acquisition risk IDU 0.69; acquisition risk non-IDU 0.7) did not impact significantly on health-state utility but level of education, age and paid employment did have an effect. Patients who had not completed secondary school had significantly lower utility scores than those who had second level or above (0.67 versus 0.73 p=0.05), utility decreased 0.003 for each additional year of age (p=0.006) and those who were in paid employment reported higher utility values than those who were not (0.76 versus 0.66 p<0.001). There was a moderately strong association between the population-derived health-state utility values and the patient self-assessed health score measured by the VAS ($R^2$ 0.46)

**Table 6-3 Health Utilities and Visual Analog Scale values for HCV disease stages in the overall cohort and with different HCV treatment histories**

| | N | Utility Score (mean (SD)) | VAS Value (mean (SD)) | Age matched Population utility value (mean (SD)) |
|---|---|---|---|---|
| **Total Cohort** | **268*** | **0.7 (0.24)** | **66 (21)** | **0.85 (0.25)** |
| • Chronic Infection | 138 | 0.74 (0.18) | 70 (18) | |
| • Compensated Cirrhosis | 26 | 0.64 (0.30) | 60 (21) | |
| • Decompensated Cirrhosis | 12 | 0.46 (0.39) | 43 (31) | |
| • Transplantation <1 year | 8 | 0.49 (0.31) | 69 (17) | |
| • Transplantation >1 year | 33 | 0.59 (0.22) | 58 (16) | |
| • HCC | 8 | 0.52 (0.39) | 38 (23) | |
| • SVR (total) | 38 | 0.81 (0.19) | 74 (21) | |
| • SVR (non-cirrhotic) | 30 | 0.80 (0.19) | 74 (21) | |
| • SVR (cirrhotic) | 8 | 0.83 (0.22) | 56 (23) | |
| • SVC | 5 | 0.72 (0.27) | 72 (17) | |
| **Treatment Naïve Cohort** | **150** | **0.67 (0.27)** | **67 (21)** | **0.91 (0.16)** |
| • Chronic Infection | 102 | 0.75 (0.19) | 71 (18) | |
| • Cirrhosis | 18 | 0.48 (0.38) | 56 (29) | |
| • Transplantation | 20 | 0.52 (0.27) | 62 (15) | |
| • HCC | 5 | 0.40 (0.38) | 38 (27) | |
| • SVC | 5 | 0.72 (0.27) | 72 (18) | |
| **Treatment Experienced Cohort** | **106** | **0.74 (0.21)** | **66 (22)** | **0.85 (0.25)** |
| • Chronic Infection | 28 | 0.76 (0.15) | 72 (16) | |
| • Cirrhosis | 16 | 0.67 (0.29) | 53 (24) | |
| • Transplantation | 21 | 0.62 (0.19) | 59 (19) | |
| • HCC | 3 | 0.72 (0.05) | 37 (23) | |
| • SVR | 38 | 0.81 (0.19) | 74 (21) | |
| Relapser | **19** | **0.75 (0.19)** | **65 (17)** | |
| • Chronic Infection | 8 | 0.82 (0.14) | 72 (18) | |
| • Cirrhosis | 6 | 0.70 (0.25) | 58 (18) | |
| • Transplantation | 4 | 0.72 (0.21) | 64 (15) | |
| • HCC | 1 | - | - | |
| Partial Responder | **11** | **0.69 (0.20)** | **71 (19)** | |
| • Chronic Infection | 7 | 0.75 (0.18) | 82 (8) | |
| • Cirrhosis | 2 | 0.78 (0.09) | 55 (28) | |
| • Transplantation | 2 | 0.41 (0.05) | 48 (4) | |
| • HCC | 0 | - | - | |
| Null Responder | **33** | **0.65 (0.21)** | **54 (23)** | |
| • Chronic Infection | 9 | 0.74 (0.13) | 65 (20) | |
| • Cirrhosis | 8 | 0.59 (0.33) | 44 (24) | |
| • Transplantation | 14 | 0.62 (0.17) | 58 (21) | |
| • HCC | 2 | 0.72 (0.07) | 30 (28) | |

*Multi-variate regression analysis*

The results of the multivariate regression model are presented in Table 6-4. Successful HCV treatment with the achievement of an SVR was associated with higher HRQOL when controlled for other variables. Less advanced liver disease and paid employment were also independently associated with higher HRQOL, while increasing years since HCV diagnosis was independently associated with lower HRQOL.

**Table 6-4 Multivariable Regression analysis to assess independent predictors of health-state utility**

| Variable | Coefficient | p-value | 95% Confidence Intervals |
|---|---|---|---|
| Constant | 0.61 | < 0.001 | 0.54, 0.69 |
| Sustained Virological Response | 0.22 | < 0.001 | 0.13, 0.31 |
| Chronic Infection(non-cirrhotic) | 0.15 | <0.001 | 0.09, 0.21 |
| Paid Employment | 0.07 | 0.03 | 0.01, 0.13 |
| Time since HCV diagnosis (years) | - 0.005 | 0.04 | -0.009, 0.00 |

*Age (in years), completion of second level education and previous transplantation were found not to be significant in this cohort when controlled for other variables. Model $R^2$=0.18*

## 6.4 Discussion

Several publications (160, 167-175) have shown that HCV infection adversely affects HRQOL and utility. In concordance with these findings, the mean utility score in this cohort is significantly lower at 0.7 (SD 0.24) than the mean utility score of a comparator UK age-matched cohort (0.85 (SD 0.25)) (180). In our study, patients with mild or moderate liver disease reported significant decrements in health-state utility when compared to age-matched UK population norms (180). The utility values for the health-states were similar to those found by others who have used the EQ-5D 3-level to calculate utility directly in this population and the values found by a meta-analysis of several studies examining this question (160, 167, 169). There has been conflicting findings with regard to differences in utility with progression of liver

disease in the previous literature (160, 168-170). Similar to Wright et al, who used the EQ-5D 3-level to estimate health utility in HCV patients, we found a significant difference in health-state utility between those patients with mild/moderate disease and those who had progressed to cirrhosis (160). Health-state utility decreased in our cohort with the progression of liver disease and time since HCV diagnosis was a significant predictor of decreased utility scores in the multivariate model. Previous publications have reported utility values based solely in ambulant populations. Our study included a small sample of inpatients with HCV-related decompensated cirrhosis representing a more advanced clinical stage than has been published in similar literature to date (160, 167-170). While the numbers are small, the inclusion of hospitalised patients in utility estimates of decompensated HCV liver disease gives a more complete picture of its impact on HRQOL and may be responsible for the difference in utility found in this cohort between patients with and without cirrhosis.

In this study, patients who had undergone liver transplantation reported higher utility scores than patients with de-compensated cirrhosis. However, the utility values reported are lower than those found in some other post-transplantation populations (181). Patients post-transplantation who have recurrence of HCV have been shown to have lower HRQOL than similar patients who are HCV-negative and they are also less likely to return to work (182). A minority of the post-transplantation cohort were in paid employment and this along with recurrent HCV infection may explain the difference in our utility values to those previously reported.

Patients who had had successful HCV treatment reported significantly higher health-utility values and self-reported health scores in both univariate and multivariate analysis. The mean utility for patients who had achieved an SVR was not significantly lower than the reported UK age-matched population norm. The choice of instrument to evaluate HRQOL can have an impact on the values found and therefore on cost-effectiveness evaluations based on those values (172). However, Hsu and colleagues reported a similar finding in their paper describing

utilities derived using the Health Utility Index 2&3 and the Short Form-6D (168). The consistency of this result across multiple instruments and populations supports HCV treatment as a worthwhile strategy in the management of HCV from the perspective of health utility. With newer agents leading to improved treatment outcomes, the possibility of shorter treatment courses and potentially interferon-free regimens, many of the current barriers to HCV treatment will be removed, although issues around affordibility may become more pronounced (11, 183).

### 6.4.1 Limitations

This study reports health-state utilities of a predominantly Northern European population of white ethnicity which may limit the ability to generalise it to cohorts who are ethnically or geographically different. However, it is similar to cohorts reported throughout Northern and Eastern Europe with a predominance of patients who give a background history of IDU and have a relatively younger age profile than traditional cohorts infected through unsafe medical practices (68, 77). As such, it provides useful information for researchers and economists developing health technology assessments for these populations. It is interesting that no significant difference was found in utility scores between patients with IDU as an acquisition risk and those who did not report IDU. This would suggest that the utility data could be applied to both cohorts. Ethnicity was not found to have a significant effect on utility scores but the numbers of non-white participants was small. We found that the mean health-state utility in our cohort was significantly lower than a UK comparator population. At the present time, there are no preference measures derived from the Irish population. UK preferences have been used as the reference values in published utility studies from Ireland in a range of different disease areas (184, 185). This study was conducted on patients attending a hospital-based hepatology service. Many HCV patients are not referred to these services if their primary care provider feels that they are unsuitable for treatment. Therefore these results may

not reflect values in cohorts that are not engaged in care. However, given the scope of the HCV epidemic, patients currently engaged in care will be those that are treated in the short to medium term and their values are the most relevant to the current discussions surrounding cost-effectiveness. Other authors have attempted to address the question of HRQOL in HCV patients who are unaware of their diagnosis (173). However, the value of this analysis lies in the rich clinical data that underpins it which would not be possible to assess in an un-engaged cohort. Paid employment had a significant effect on utility values in the multivariate analysis and there were more people in paid employment in the SVR group than in those who did not have an SVR. However, as SVR was independently associated with higher utility in the multivariate analysis we feel that this is unlikely to be of significance. Despite increasing our sample size, there were relatively few patients in the rarer health-states such as decompensated cirrhosis and HCC and this is likely to have affected our power to detect a significant effect on HRQOL. This is true of all HCC utility data published in the literature (167-172). The primary aim of the study was to establish estimates of utility and the uncertainty around those estimates is validly presented. A strength of the HCC data is that all patients had underlying HCV infection. This is in contrast to some previous publications where the underlying diagnosis of HCC patients was heterogeneous, due to difficulty with case-finding (169).While acknowledging these limitations, this study gives health-state utility data derived using the same methodology, across the full spectrum of HCV disease. It reports rich clinical, demographic and HRQOL data on proportionately large numbers of post-transplantation, cirrhotic and treatment-experienced patients and all patients in these health-states have a background of HCV infection.

## 6.5 Conclusion

This study indicates that Irish HCV patients who achieve an SVR, report utilities equivalent to HCV-negative age-matched populations. The health-state utilities presented here, which have been derived with the most up-to-date utility instrument, will be used as inputs in the cost-utility model in Chapter 8.

# Chapter 7

# 7 The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of HCV Genotype 1

## 7.1 Introduction

Dual therapy with pegylated-interferon and ribavirin given for 48 weeks was regarded as the standard of care for treating HCV genotype 1 infection for the past decade (12, 81). This resulted in successful treatment outcomes, known as a sustained virological response (SVR) in 40-50% of those with genotype 1 infection that were treated (10, 82, 83). The licensing of two new HCV protease inhibitors, telaprevir and boceprevir, heralds a new era in the treatment of HCV genotype 1 infection (186). The addition of these agents to the standard-of-care regimen of pegylated interferon and ribavirin results in a significant increase in SVR rates in patients with genotype 1 infection and allows a proportion to be treated for a shorter duration (94-97, 142, 186-191). It is likely that this will lower the threshold for treating substantial numbers of patients with HCV infection. As yet there are no head to head comparative trials to identify whether there are differences in efficacy between the protease inhibitors. Network meta-analysis, or mixed treatment comparison, allows calculation of the relative efficacy of treatments in the absence of head-to-head evidence. This is an extension of standard meta-analysis which is used to combine studies looking at a single intervention.

A Bayesian approach is often adopted since it is well suited to the complex evidence structures that arise (192). Bayesian hierarchical models simultaneously estimate the relative efficacy between treatments that have not been directly compared, and provide the most flexible approach to indirect comparison modelling. The technique was first introduced by Lu and Ades in 2004 (193, 194), and has since become a standard tool in such applications where multiple treatments for a given condition exist (195). The outcome of a Bayesian analysis is a posterior

probability distribution for each parameter of interest. These can be summarised by the mean and a credible interval to capture the uncertainty surrounding the estimate.

A mixed treatment comparison using this methodology was undertaken to determine the relative differences in efficacy between boceprevir and telaprevir when used as a third agent in HCV genotype 1 treatment. The results were utilised as the efficacy inputs for the model in Chapter 8.

## 7.2 Methods

### 7.2.1 Systematic Review

A review protocol was developed along with pre-specified inclusion criteria using a PICOS structure (196). *(Table 7-1)* Medline/PubMed, Embase, The Cochrane Library and Science Citation Index were searched on 1st of November 2011 and the searches re-run on the 3rd of September 2012. In an effort to reduce the effect of publication bias and to include "grey literature" (i.e. research that has not been published as journal articles), a hand-search of conference abstracts from the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases conferences (AASLD) (Digestive Diseases Week and the Liver Meeting) in 2010, 2011 and 2012 was performed. Details of the search strategy can be found in Appendix 3. The first decision for inclusion was made by two reviewers (JK and SS) on the basis of title and abstract. For studies that appeared to meet the inclusion criteria the full text was sourced and assessed.

**Table 7-1 Summary of inclusion and exclusion criteria for the meta-analysis**

| Category | Details |
|---|---|
| **Population** | Studies of patients over the age of 18 chronically infected with HCV genotype 1 |
| **Sub-population** | 1. Patients with chronic HCV genotype 1 infection who were treatment naïve<br>2. Patients with chronic HCV genotype 1 infection who were treatment experienced. |
| **Intervention** | Studies where patients were treated with pegylated interferon and ribavirin in combination with either telaprevir or boceprevir.<br>Study arms which evaluated telaprevir or boceprevir for unlicensed durations or without both pegylated-interferon and ribavirin at standard doses were excluded. |
| **Outcomes** | Rates of sustained viral response (SVR) in patients receiving pegylated-interferon and ribavirin in combination with either telaprevir or boceprevir |
| **Study Design** | Randomised controlled trials of human subjects that have undergone peer-review either for journal publication or for abstract presentation at a major Hepatology scientific conference. |
| **Language** | No language limits |
| **Subgroups considered** | 1. Patients with chronic HCV genotype 1 infection who were treatment naïve and had black ethnicity<br>2. Patients with chronic HCV genotype 1 infection who were treatment experienced and had a prior treatment response classified as "relapse". |

Study selection followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which consist of a 27 point check-list and a 4-phase flow diagram (196, 197). *(Figure 7-1)* Quality of the included studies was assessed using the Cochrane Collaboration "Risk of bias" tool (198). *(Figure 7-2)* A sensitivity analysis was performed, where the trials of lesser quality were removed and the analysis re-run.

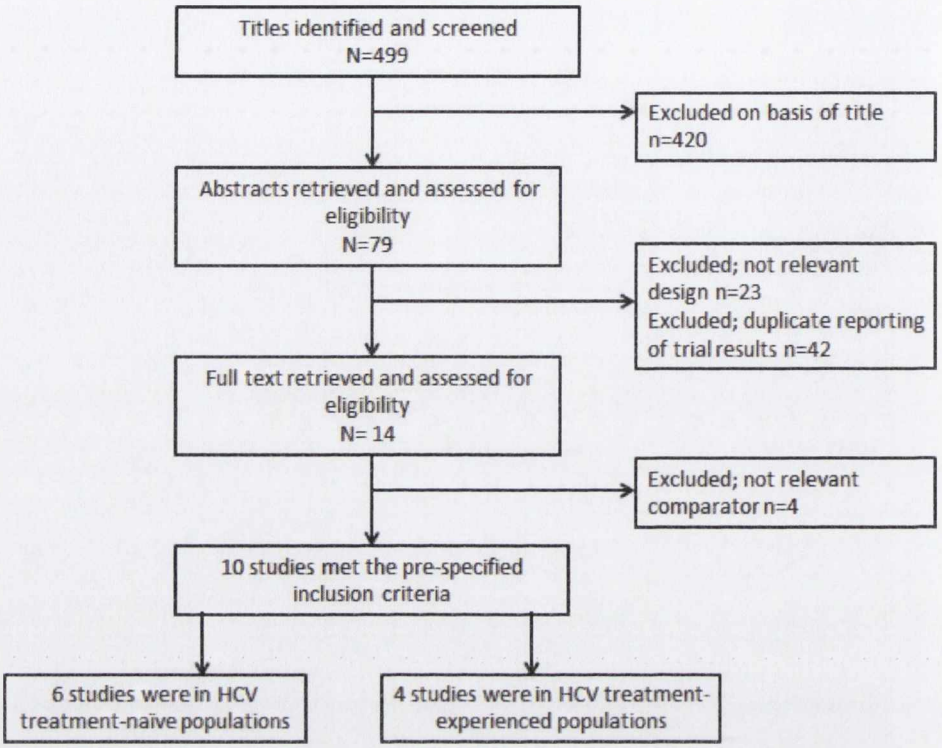



**Figure 7-1 Flow diagram of literature search for mixed treatment comparison meta-analysis**

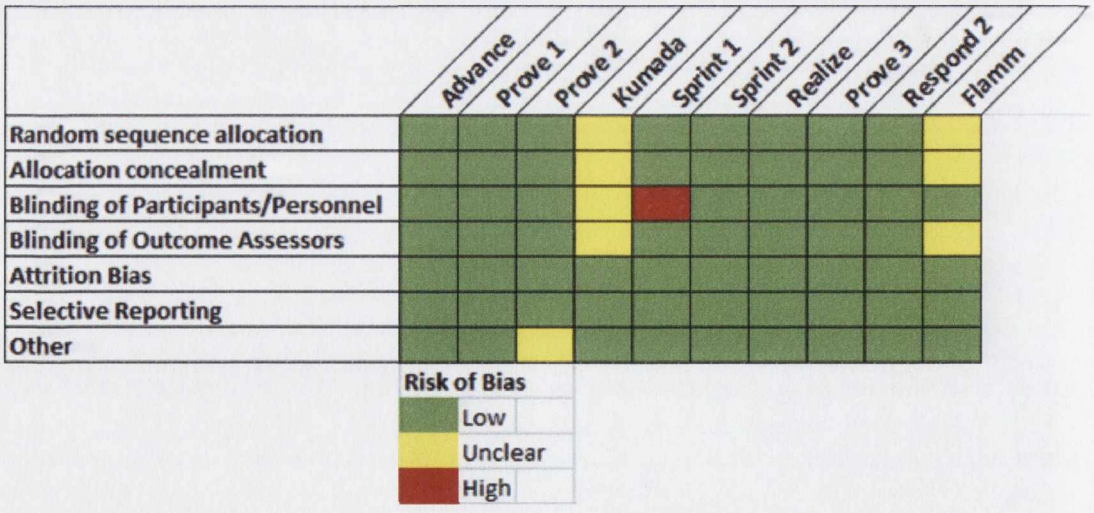



**Figure 7-2 "Risk of Bias" summary of trials included in the meta-analysis**

Meta-analyses were planned in two patient populations: (1) Patients with chronic HCV genotype 1 infection who were treatment-naïve and (2) Patients with chronic HCV genotype 1 infection who were treatment-experienced. As IL-28B or other host-related markers of interferon responsiveness were not recorded routinely in the clinical trials, two subgroup analyses of the populations studied were planned as surrogate markers for interferon responsiveness. In the treatment-naïve group, there was a pre-specified sub-group analysis of patients with black ethnicity. Prior treatment response is likely to be the most important predictor of future treatment response in treatment-experienced patients (199). Therefore, a pre-specified subgroup analysis of prior treatment "relapsers" versus those whose prior treatment response was otherwise classified was performed. Patients were classified in this way due to inconsistencies in the definitions of prior partial and null-response between the trials, which limited correlations across trials in these patients. Given the recent licensing of these medications, publication bias is difficult to assess. The number of trials is too small to draw meaningful conclusions from a funnel plot, which is therefore not presented. The WHO Clinical Trials registry portal and ClinicalTrials.gov were examined and no evidence was found of registered trials that appeared to be delayed in their reporting.

### *Data Extraction*

Data were extracted from published journal articles and conference reports using standardised data collection forms. If required data was not available in the article/conference abstract, supplemental appendices were examined. Additional information was sought directly from five authors, four of whom replied. This allowed analysis of the quality of the studies and access data that was not available from the publications. Data were extracted by the thesis author and all data used in the meta-analysis was cross-checked with the second researcher (Dr. Suzanne Schmitz, Department of Statistics, Trinity College Dublin). Any discrepancies in the extracted data were resolved by reference to the original source material.

Data were extracted on pre-specified baseline demographics and clinical characteristics of patients in addition to baseline viral characteristics such as viral load and genotype subtype which may act as potential confounders (198). Data were extracted on the number of patients in each arm of the trial and relative frequency of sustained virological response. Study arms which evaluated telaprevir or boceprevir for unlicensed durations, or without both pegylated-interferon and ribavirin at standard doses were excluded. All articles reported intention-to-treat results and these were utilised. In the trials of treatment-naive patients, data were extracted for numbers of patients with black ethnicity. The number of patients with black ethnicity in PROVE-2 (n=3) and the trial by Kumada et al (n=0) were small and separate SVR rates for this subgroup were not available. Therefore, these studies were excluded from the subgroup analysis of black ethnicity (95, 189). There was no other missing data. For patients who were treatment-experienced, data were extracted on numbers who were enrolled in the trials as prior treatment "relapsers" and those who were not. A description of the trials and data extracted is presented in Table 7-2.

**Table 7-2 Summary of trials included in the mixed treatment comparison presenting data used in the meta-regression of potential confounders and the subgroup analysis**

| Study | Population Characteristic and Number | Intervention | HCV viral load >800,000iu/ml N (%) | Black cohort N (%) | Prior Relapse N (%) | HCV 1a N (%) | Cirrhotic N (%) | Relapse rates N (%) | SVR N (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Advance** | Treatment naïve<br>N=724 | Telaprevir + PR n= 363<br>PR n=361 | 281 (77)<br>279 (77) | 26 (7)<br>28 (8) | N/A | 213 (59)<br>208 (58) | 21 (6)<br>21 (6) | 17/264 (65)<br>51/189 (27) | 271 (75)<br>158 (44) |
| **PROVE 1** | Treatment naïve<br>N=233 | Telaprevir +PR n=158<br>PR n=75 | 134 (85)<br>69 (92) | 15 (9)<br>9 (12) | N/A | 101 (64)<br>50 (67) | excluded | 4/92 (4)<br>8/35 (23) | 101 (64)<br>31 (41) |
| **PROVE 2** | Treatment naïve<br>N=163 | Telaprevir +PR n=81<br>PR n=82 | 73 (90)<br>68 (83) | 1 (1)<br>2 (2) | N/A | 31 (38)<br>25 (43) | excluded | 8/57 (14)<br>10/45 (22) | 56 (69)<br>38 (46) |
| **Kumada** | Treatment naive<br>N=189 | Telaprevir +PR n=126<br>PR n=63 | 26 (21)<br>18 (29)<br>*(>700,000iu/ml)* | 0<br>0 | N/A<br>N/A | 2 (1.2)<br>0 (0) | excluded | 21/113 (19)<br>14/45 (31) | 92 (73)<br>31 (49) |
| **SPRINT 1 Part 1** | Treatment naïve<br>N=310 | Boceprevir +PR n=206<br>PR n=104 | 183 (89)<br>94 (90)<br>*(>600,000iu/ml)* | 30 (15)<br>16 (15) | N/A | 113 (55)<br>53 (51) | 13 (6)<br>8 (8) | 20/160 (13)<br>12/53 (23) | 135 (66)<br>39 (38) |
| **SPRINT 2** | Treatment naïve<br>N=1097 | Boceprevir +PR n=734<br>PR n=363 | 627 (92)<br>308 (85) | 107 (15)<br>52 (14) | N/A | 471 (64)<br>227 (63) | 76 (10)<br>24 (7) | 48/522 (9)<br>39/176 (22) | 475 (65)<br>137 (38) |
| **REALIZE** | Treatment experienced<br>N=662 | Telaprevir +PR n=530<br>PR n=132 | 472 (89)<br>114 (86) | 19 (4)<br>11 (8) | 286 (54)<br>68 (51) | 239 (45)<br>59 (45) | 139 (26)<br>30 (23) | 52/214 (13)<br>33/51 (65) | 346 (65)<br>22 (17) |
| **PROVE 3** | Treatment experienced<br>N=229 | Telaprevir +PR n=115<br>PR n=114 | 106 (92)<br>104 (91) | 9 (8)<br>10 (9) | 42 (37)<br>41 (36) | 69 (60)<br>71 (62) | 19 (17)<br>13 (11) | 22/80 (27)<br>17/33 (52) | 59 (51)<br>16 (14) |
| **RESPOND 2** | Treatment experienced<br>N= 403 | Boceprevir +PR n=323<br>PR n=80 | 288 (89)<br>65 (81) | 37 (11)<br>12 (15) | 208 (64)<br>51 (64) | 190 (59)<br>46 (58) | 39 (12)<br>10 (13) | 36 /238 (15)<br>8/25 (32) | 202 (63)<br>17 (21) |
| **Flamm et al** | Treatment experienced<br>N=201 | Boceprevir +PR n= 134<br>PR n=67 | 101 (75)<br>54 (81) | 12 (9)<br>8 (12) | 36 (27)<br>47 (70) | 75 (56)<br>38 (57) | 32 (24)<br>15 (22) | 11/95 (12)<br>7/21 (33) | 86 (64)<br>14 (21) |

*Abbreviation: PR = pegylated interferon and ribavirin*

### 7.2.2 Statistical analysis

The analysis was conducted using a Bayesian mixed treatment comparison model. The included trials provide the underlying evidence structure for this analysis which is shown in the network diagram in Figure 7-3. Models were fitted separately for two patient populations: Treatment-naive patients and treatment-experienced patients. A subgroup analysis for black ethnicity was conducted in the naive patient group. In the experienced group, "relapsers" and "non-relapsers" were analysed as subgroups. A post-hoc analysis of differences in relapse rates for patients who achieved an end-of-treatment response was also performed. As there are only a small number of trials for each drug, and in the absence of marked heterogeneity (Table 2, last column), a fixed effects model for the treatment effect was used. The influence of three potential confounders, baseline HCV viral load, HCV genotype subtype and presence of cirrhosis, were analysed in a meta-regression model to identify if they were effect modifiers (200). The models calculate odds ratios (ORs) of one treatment relative to another. All models were fitted in WinBUGs®, a software package using Markov chain Monte Carlo techniques (193, 201). The code can be accessed in Appendix 3. The statistical analysis was performed by Dr. Suzanne Schmitz, Department of Statistics, Trinity College Dublin. All other aspects of the meta-analysis were performed by the thesis author.

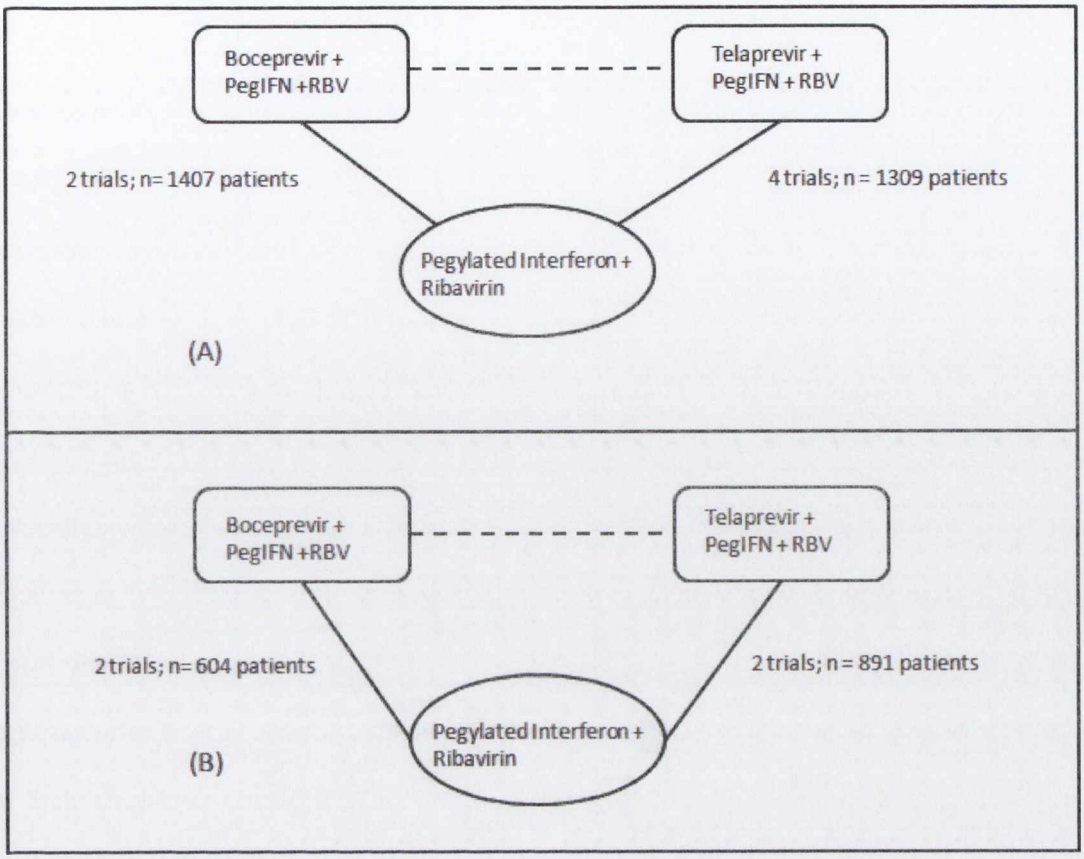



**Figure 7-3 Network diagrams for mixed treatment comparisons**

**(A) Network diagram for mixed treatment comparison in HCV treatment-naïve patients**

**(B) Network diagram for mixed treatment comparison in HCV treatment-experienced cohorts**

## 7.3 Results

Of the 499 studies identified by the literature searches, 10 studies met the inclusion criteria (94-97, 142, 187-191). Six studies related to treatment-naïve patients, and 4 to treatment-experienced patients. The study characteristics along with patient numbers, treatment arms and potential confounding variables are presented in Table 7-2. Baseline demographic, clinical, and viral parameters were similar across the trials. The meta-regression found none of the potential confounders to be effect modifiers. Therefore, they were not included in the final model.

### 7.3.1 Treatment-naïve patients

Six studies met the criteria for analysis in HCV genotype 1 infected treatment-naïve patients (94, 95, 187-190). In the total treatment-naive population (n=2716) the addition of boceprevir to a backbone therapy of pegylated interferon and ribavirin resulted in more efficacious treatment than pegylated interferon and ribavirin alone (OR 3.06 95% CI (2.43, 3.87)). Similarly, the addition of telaprevir to a backbone therapy of pegylated interferon and ribavirin resulted in more efficacious treatment than pegylated interferon and ribavirin alone (OR 3.24 95% CI (2.56, 4.10)). There was insufficient evidence to detect a difference between telaprevir and boceprevir when added to standard of care (OR 1.06 95% CI (0.75, 1.47)). When patients with black ethnicity were considered (n=283, boceprevir n=205, telaprevir n=78), increased efficacy with either of the triple therapy regimens compared to standard of care was also observed (boceprevir versus SOC OR 3.58 95% CI (1.84, 7.31); telaprevir versus standard of care OR 5.99 95% CI (2.17, 17.87)). The model did not detect a significant difference in efficacy between either triple therapy regimen in this sub-population (telaprevir versus boceprevir OR 1.67, 95% CI (0.48, 6.05)). Results are summarised in Figure 7-4.

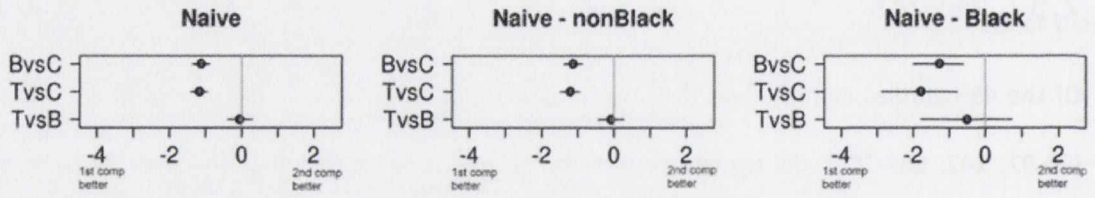



**Figure 7-4 Graph for pair-wise odds ratio of relative treatment effects in the overall treatment-naïve population and the subgroup analysis of treatment-naïve black and non-black populations**

*B=Boceprevir, T=Telaprevir, C= standard of care (pegylated interferon and ribavirin) Comp = comparator*

### 7.3.2 Treatment-experienced patients

Four studies met the criteria for analysis in the HCV genotype 1 infected treatment-experienced patient population (96, 97, 142, 191). In the overall treatment-experienced population (n=1495), there was a significant improvement in SVR when the regimens including boceprevir were compared to standard of care (OR 6.53 95% CI (4.20, 10.32)) and when regimens containing telaprevir were compared to standard of care (OR 8.32 95% CI (5.69, 12.36)). There was insufficient evidence to detect a difference in SVR between those regimens utilising telaprevir as their third agent and those utilising boceprevir as their third agent (OR 1.27 95% CI (0.71, 2.30)).

In the model considering those patients who had prior treatment relapse (n=841), there was a significant difference in efficacy which favoured telaprevir (telaprevir versus boceprevir OR 2.61 95% CI (1.24, 5.52)). Both agents were significantly better than standard of care (boceprevir versus standard of care OR 6.25 95% CI (3.79, 10.53); telaprevir versus standard of care OR 16.31 95% CI (9.52, 28.51)). In patients who did not have a prior treatment relapse (n=654) there was no significant difference in efficacy detected between telaprevir and boceprevir (OR 0.44 95% CI (0.09, 1.72)). Results are summarised in Figure 7-5.

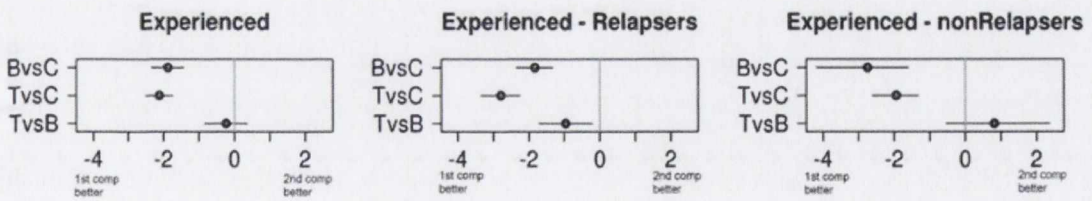



**Figure 7-5 Graph for pair-wise odds ratio of relative treatment effects in the overall treatment-experienced population and the subgroup analysis of treatment-experienced "relapsers" and "non-relapsers".**

*B=Boceprevir, T=Telaprevir, C= standard of care (pegylated interferon and ribavirin) Comp = comparator*

*On-treatment analysis of relapse rates*

For treatment-naive patients, no difference was detected in relative relapse rates between patients who received a telaprevir based regimen and those who received a boceprevir based regimen (OR -0.34 95% CI (-0.53, 0.22)).

For patients who were treatment-experienced, patients treated with telaprevir had a lower relative rate of relapse than those treated with boceprevir (OR -0.91 95 CI (-1.78, -0.03)).

### 7.3.3 Sensitivity Analysis

With the exclusion of the trials with an increased risk of bias (PROVE-2 and Kumada for the treatment-naive analysis; Flamm et al. in the treatment-experienced analysis), the sensitivity analysis resulted in increased credible intervals in all analyses performed, as would be expected from the smaller numbers. The improved outcome observed with telaprevir over boceprevir in treatment experienced "relapsers" remained (OR 2.64 CI (1.09, 6.30)). There was no change to the findings in the other analyses.

## 7.4 Discussion

The enhanced clinical efficacy with the addition of protease inhibitors to the standard of care has been clearly demonstrated in the randomised controlled trials published to date (94-97, 142, 187-191). They have shown an improvement in treatment outcomes across a broad range of patient populations, both treatment-naïve and treatment-experienced. As a result of these favourable clinical trial outcomes, these agents are currently being assessed in many health care systems from the perspective of their cost effectiveness. The comparative effectiveness of these agents is germane to the analysis under consideration in both pharmacoeconomic and clinical forums as decisions are made between agents in relation to funding and individual prescribing. The ideal method of addressing the question of which agent is more effective would be a head-to-head non-inferiority trial. This would enable us to control for the differences between the telaprevir and boceprevir trials in relation to their use of different

interferons, dosing strategies for ribavirin and use of anti-anaemics. However, a search of the registries Clinicaltrials.gov, WHO clinical trials registry portal and International Standard RCT network, revealed 177 registered trials for telaprevir and boceprevir, none of which was a head-to-head trial. In the absence of a non-inferiority trial in the foreseeable future the present analysis provides useful and relevant estimates of relative efficacy between these agents.

The analysis found an improvement in the rates of SVR achieved with telaprevir over boceprevir in patients who have had a prior treatment relapse. Potential difficulties with isolating the efficacy of the individual protease inhibitors include patient tolerance to and adherence with pegylated interferon and ribavirin. Relapsed patients have previously tolerated full-courses of pegylated interferon and ribavirin with an end-of-treatment response which lessens these concerns. Therefore, the differences in effect seen in this population may better reflect the differences between the individual protease inhibitors with less confounding from tolerance issues to pegylated interferon and ribavirin than that seen in other patient populations. Treatment duration is also an important factor with regards to choice of agent for this population. The total treatment duration for response-guided therapy with telaprevir is shorter (24 weeks) than boceprevir (36 weeks in the U.S., 48 weeks in Europe) which has cost and tolerance implications (12, 81). A post-hoc analysis of patients with an end-of-treatment response and a subsequent relapse was performed to further analyse the difference seen in the treatment-experienced population. This found a reduced relative rate of relapse in patients treated with telaprevir, which may explain some of the difference found in the "relapse" subgroup. Unfortunately, the data on relapse rates by previous treatment response was not reported for all trials, so no further analysis was possible. There are relatively small numbers of trials available for analysis at the present time, particularly in treatment-experienced patients, and future studies will be helpful to further elucidate this relationship.

While the RCTs included patients who have historically been less susceptible to treatment with interferon and ribavirin, such as those who are black, the numbers were low. However, the overall magnitude of the treatment effect was greater in the naïve black subgroup than that seen in the overall population. In the subgroup of treatment-experienced "non-relapsers" the magnitude of the treatment effects of the new regimens over the standard of care is also greater than that seen in the overall population. It is possible that the proportional benefit gained from the new agents is greater in those who are less interferon responsive, than those who are most interferon responsive. This would support the subgroup analysis of SPRINT-2 which revealed little difference in SVR rates in patients who were treatment-naive, non-cirrhotic with a CC IL-28B subtype between those treated with pegylated-interferon and ribavirin and those given triple therapy (202). It may be reasonable to offer some patients who fall into this category and achieve a rapid virological response, the option to continue on pegylated interferon and ribavirin alone, given the additive side-effects and costs of the protease inhibitors.

## 7.5 Limitations

The most robust way to evaluate this question would be a head-to-head randomised controlled non-inferiority trial. At the present time, there is no plan for such a trial. Therefore, this analysis provides the best available estimates of relative efficacy. The mixed treatment comparison performed does not detect a significant difference in treatment outcomes between the two agents for the primary comparisons. The credible intervals for the estimated effects are wide, indicating remaining uncertainty. This highlights the need for additional data to accurately determine the size of the difference between these treatments, rather than there being no difference.

This analysis only included data from randomised controlled trials. Effectiveness in the standard clinical setting may not correlate with that seen in clinical trials. As these agents

become more widely used it is important that real world effectiveness data should be analysed. The establishment of outcomes registries would facilitate this. The small number of patients in certain important clinical subgroups, such as those with cirrhosis, precluded their separate consideration in this analysis. Individual trial data indicate that they have improved outcomes with the new agents compared to standard of care (94-97, 142, 187-191). The incidence of adverse effects such as rash and anaemia may have an impact on the cost of and adherence to therapies, however only efficacy is considered in this analysis.

The meta-regression found none of the potential confounders to be effect modifiers. The relative frequencies of the confounders were very similar across trials and in this study they were analysed at the aggregate level rather than at the patient level. These factors may explain why they were not found to be significant. (Table 7-2).

## 7.6 Conclusion

The analysis does not detect a significant difference in treatment outcomes between the two agents in the overall treatment-naive or treatment-experienced populations. However, in patients with a history of prior treatment relapse, telaprevir has greater relative efficacy. As these patients have the potential for 24 weeks of therapy when treated with telaprevir, it would appear to be the optimal choice in this subgroup. This study was not able to provide estimates of relative efficacy for patients with cirrhosis due to limited trial data. The results of currently underway studies, may allow such analysis in the future. In the absence of head-to-head non-inferiority trials, these estimates of relative efficacy will be of use to decision makers involved in cost-effectiveness assessments, and to clinicians when considered with clinical parameters in the setting of individual patient treatment pathways. They are used as the efficacy inputs for the model presented in the following chapter.

# Chapter 8

# 8 The Economic Evaluation of Treatments for Hepatitis C in Ireland

## 8.1 Introduction

Decision analytical modelling is an approach that has been used in many areas of healthcare to establish estimates of the cost-effectiveness of new and existing therapies and technologies. It provides a long-term outlook of healthcare costs and gains, extrapolating from available short-term data. It is an approach that is very suitable to examine a disease area such as Hepatitis C, given the chronic nature of the disease (106). The standard of care treatment has been pegylated interferon and ribavirin, however the decision to reimburse this treatment was made prior to the advent of health technology assessment in Ireland. The licensing of two new protease inhibitors for HCV treatment, boceprevir and telaprevir, and the imminent arrival of many more novel high-cost HCV therapies prompted the initiation of this research. Individual health technology assessments of the two agents compared to standard of care of pegylated Interferon and ribavirin were undertaken prior to re-imbursement decisions in 2012 by the National Centre for Pharmacoeconomics, however they have not been compared against each other in the Irish setting (99, 100). These were based on industry sponsored models and did not include a "No treatment" option. This is the first independently produced model in Ireland to directly compare the cost-utility of treatment with boceprevir and telaprevir and the first to evaluate pegylated interferon and ribavirin treatment. At the beginning of this project there was no data available on the cost of HCV care or the HRQOL of patients with different stages of HCV-related liver disease in Ireland. This model is populated with costs and health utilities derived from an Irish population. It is particularly timely given the slew of new agents in this disease area that are being submitted for reimbursement assessment at the present time. Building onto this model will allow the National Centre for Pharmacoeconomics to

independently evaluate the cost-effectiveness of these agents as they are submitted for assessment.

## 8.2 Aims

The aim of this project was to develop a hybrid model to examine the cost utility of the reimbursed agents for treating Hepatitis C Genotype 1 in Ireland in 2013.

Objectives included:

- Construction of a decision tree to accurately reflect the typical course of a patient receiving HCV treatment
- Construction of state-transition (Markov) models to accurately reflect the natural history of a patient with ongoing viral infection with Hepatitis C and to reflect the course of a patient "cured" of HCV
- Application of estimates of the epidemiological profile of patients infected with Hepatitis C in Ireland, derived from existing data sources *(Chapter 4)*
- Application of relative efficacy estimates of telaprevir, boceprevir and pegylated interferon derived from a network meta-analysis *(Chapter 7)*
- Application of the cost estimates for care of an Irish patient with HCV-related liver disease *(Chapter 5)*
- Application of the utility estimates for Irish patients with HCV-related liver disease *(Chapter 6)*

## 8.3 Methods

### 8.3.1 Description of the Hybrid model

The model was built using TreeAge software.

### *Structure of the Decision Tree*

The patient enters the model at a decision node with 4 branches:

- No treatment
- Treatment with pegylated interferon and ribavirin
- Treatment with pegylated interferon, ribavirin and telaprevir
- Treatment with pegylated interferon, ribavirin and boceprevir

Patients in the treatment arms encounter chance nodes which distribute them between

- Cirrhosis/No Cirrhosis (all arms)
- Rapid Virological Response/ No Rapid Virological Response (telaprevir and boceprevir no cirrhosis arms only)
- Development of anaemia/no anaemia (treatment arms)
- Early discontinuation/complete full course of treatment (treatment arms)
- Aquisition of a sustained viral response/ No sustained virological response (treatment arms)

The duration of the decision tree is 72 weeks to model the duration of a typical course of Hepatitis C treatment, followed by a six month period of follow-up prior to the assessment of a sustained viral response or "cure". Patients accumulate the costs and QALYs associated with their decision arm prior to moving into the state-transition portion of the model, where they remain for the rest of the model.

The decision tree is presented graphically in Figures 8.1 and 8.2 below

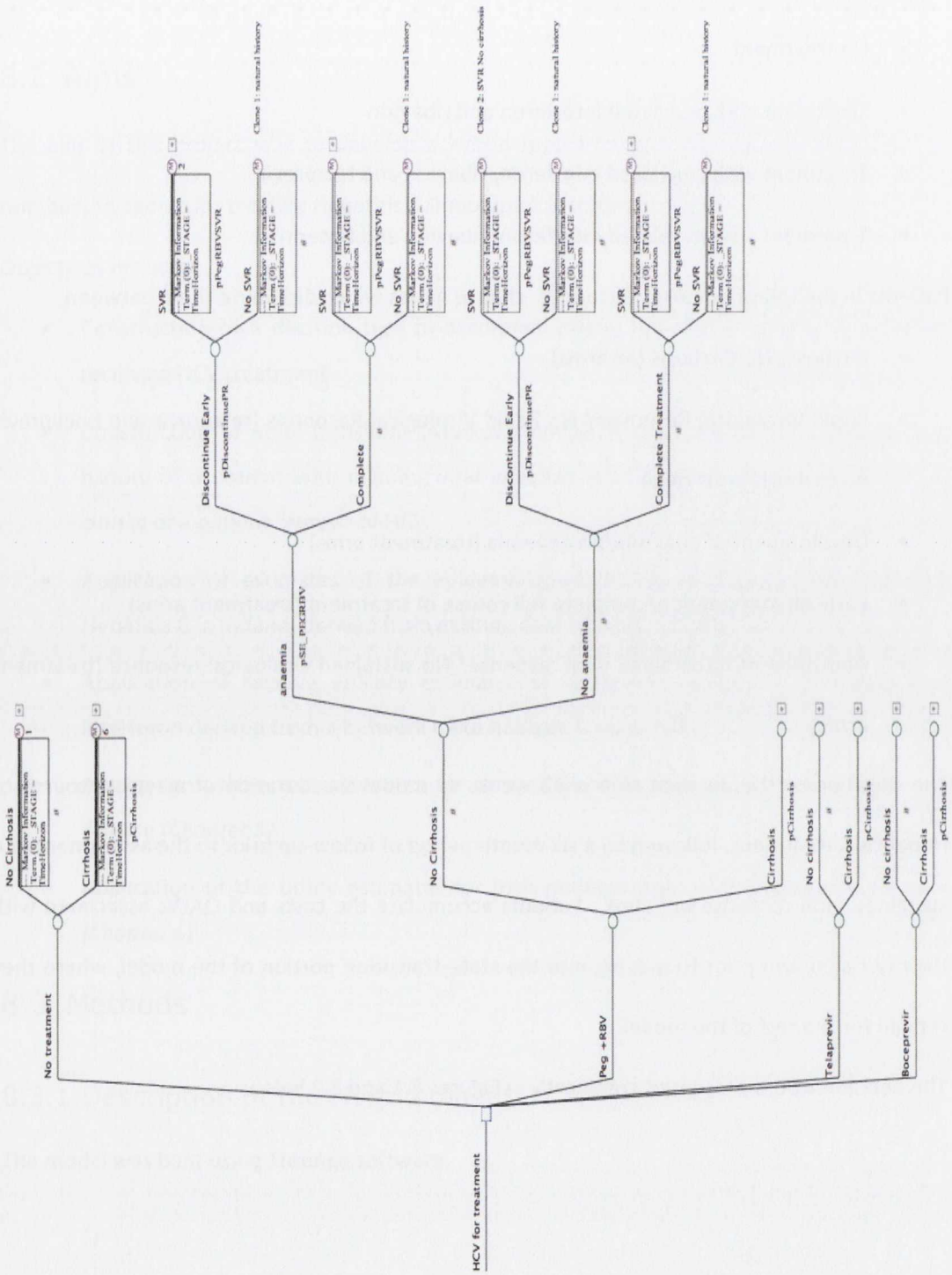



**Figure 8-1 Outline of Decision Tree**

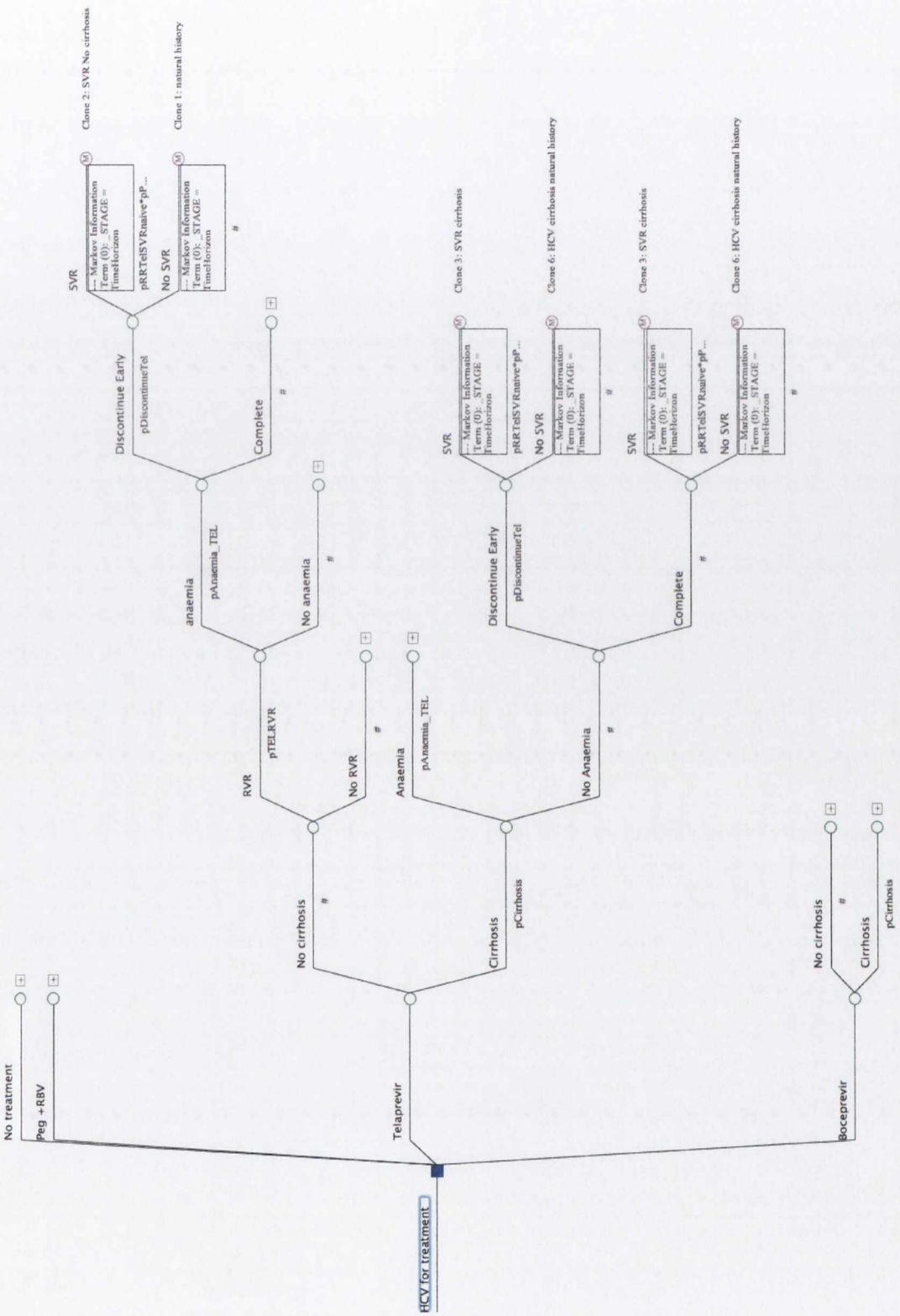



**Figure 8-2 Outline of fully expanded Protease Inhibitor treatment arm**

### *State-Transition (Markov) Model*

There are 4 different State-transition models included in the model to model the progression of patients depending on whether or not they have cirrhosis on entry to the model and for those in the treatment arms, whether or not they achieve a sustained viral response. Patients progress from less severe to more severe health states depending on the transition probabilities. Backward progression is not allowed. Patients can die from background mortality in all healthstates.

- Markov 1: Natural History of Hepatitis C infection (no cirrhosis)
- Markov 2: Natural History of Hepatitis C infection (cirrhosis)
- Markov 3: Sustained virological response (no cirrhosis)
- Markov 4: Sustained virological response (cirrhosis)

In Markov 1, there are 10 different health states (Figure 8-3). Patients are initially distributed between the Mild and Moderate healthstates as per epidemiological data from the National HCV database.

Markov 2 is an adaptation of Markov one (Figure 8-4). It does not include the Mild and Moderate health states as all patients are entering with cirrhosis. They are initially distributed between compensated and decompensated cirrhosis based on epidemiological data from the National HCV database.

Markov 3 (Figure 8-5) represents the course of patients who have been cured of Hepatitis C and do not have significant underlying liver fibrosis. It is assumed that they will not develop any further liver disease and that their mortality will mimic that of the background population. They remain in yearly follow-up as this is currently clinical care in Ireland.

Markov 4 represents the course of patients who have been cured of Hepatitis C but have significant underlying fibrosis at the time of their treatment. This Markov is an adaptation of Markov 2 (Figure 8-4). These patients remain at risk of progression of their liver disease although the rates of decompensation and hepatocellular carcinoma have been shown to be

significantly lower in patients who have been treated for HCV and therefore the transition probabilities are adjusted to reflect this (203). The outcomes of liver transplantation in patients who are HCV negative are similarly better than in those who are HCV–infected and those transition probabilities have been adjusted accordingly (204).

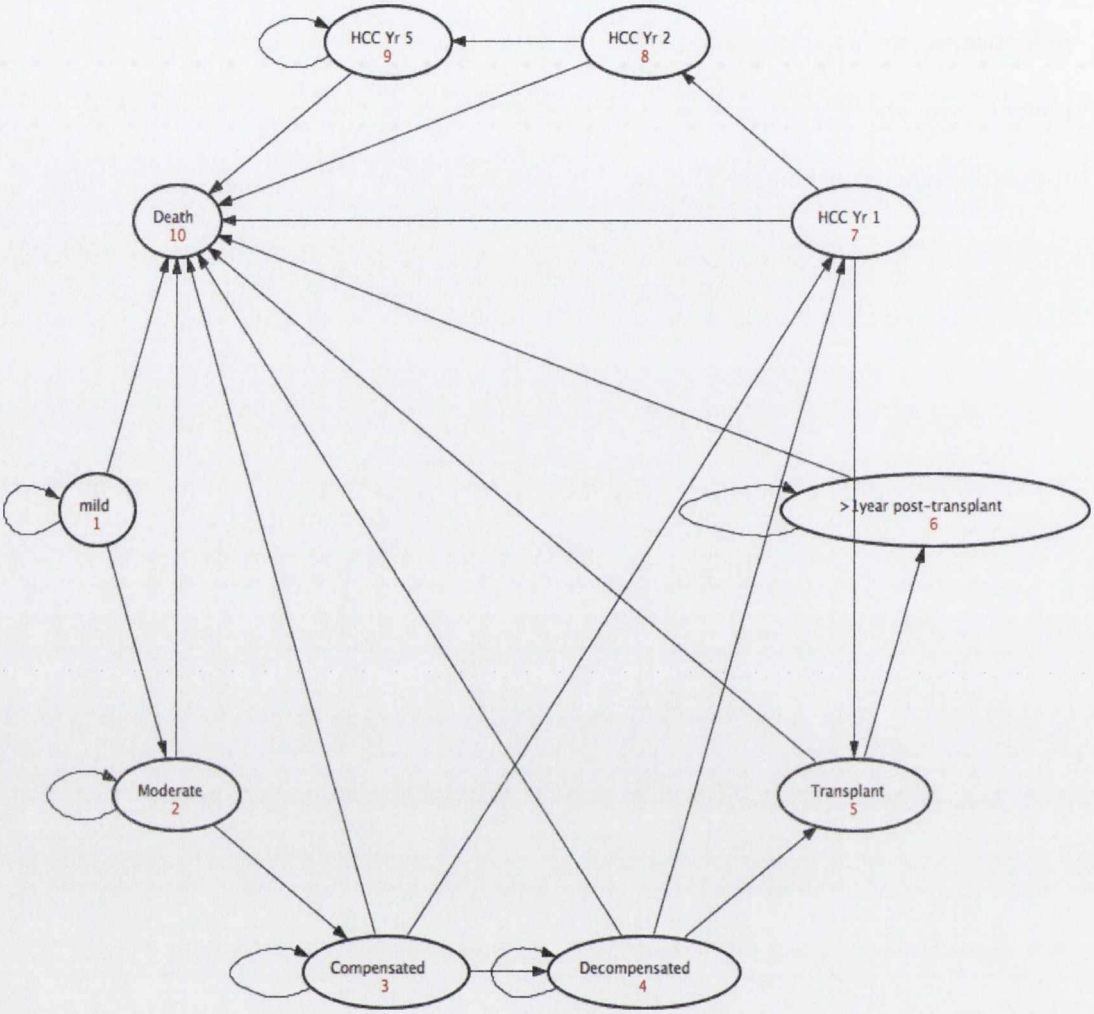



**Figure 8-3 Markov 1 Natural History of Hepatitis C**

Patients enter the model in either the Mild or Moderate Health state

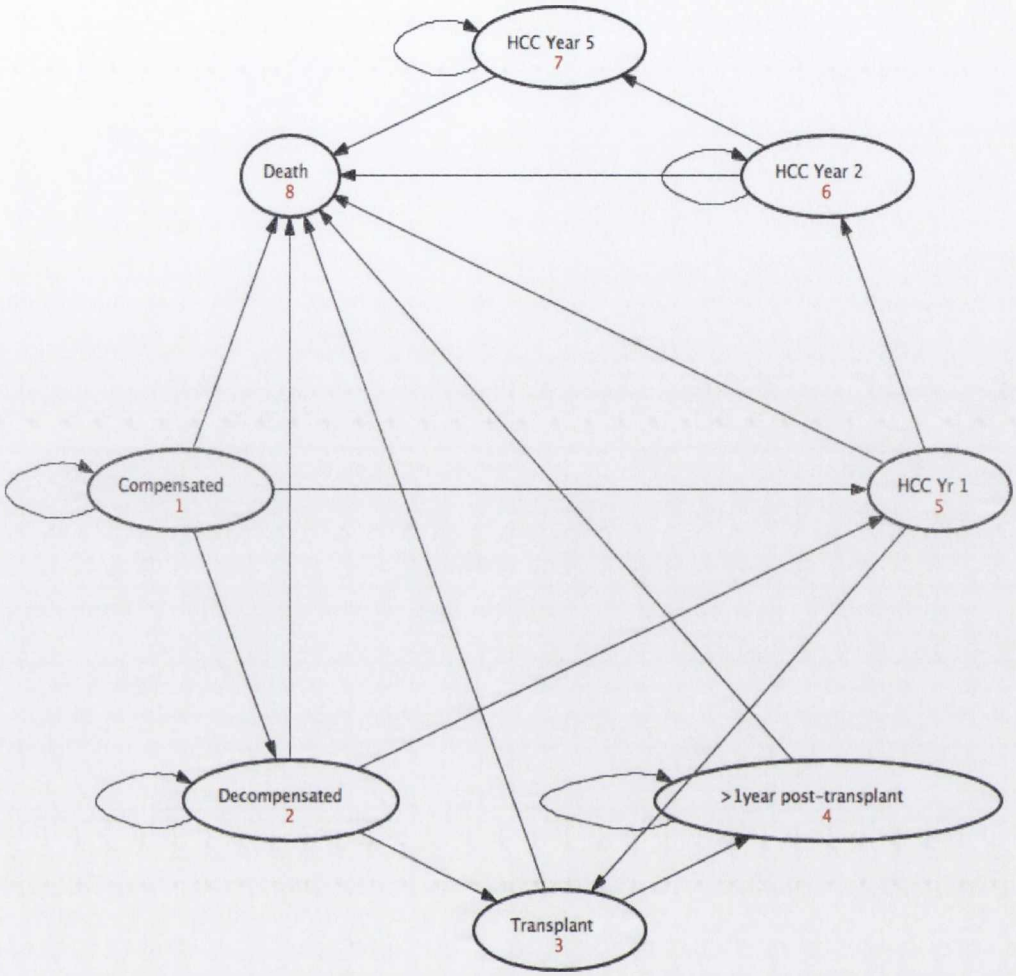



**Figure 8-4 Markov 2 and 4: Natural History of HCV patients entering the model with cirrhosis**

Patients in the Treatment arms of the model enter the cirrhosis Markov in the compensated health state. Those in the Natural History arm, enter in both the compensated and decompensated health states

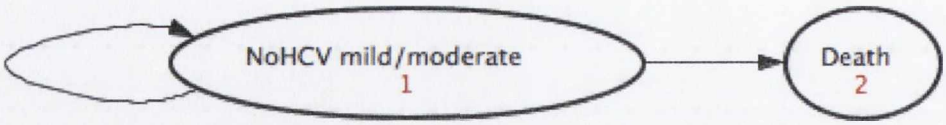



**Figure 8-5 Markov 3: Patients without cirrhosis at the time of HCV treatment who obtain a sustained virological response**

### *Structural Assumptions*

There are a number of assumptions built into this model

- Progression is unidirectional. Patients can only progress forwards to more severe disease states and cannot return to milder forms of liver disease. This is a conservative approach as occasionally patients who have received HCV treatment but failed to achieve an SVR show an improvement in their fibrosis level post-treatment, but it is consistent with natural history cohort data from the National HCV database (69).
- The model does not allow for re-treatment of Hepatitis C in the event of treatment failure. Analysis of PCRS data related to HCV treatment from 2001-2012 suggested that only 3% of patients underwent re-treatment courses *(Chapter 4)*. Thus, a single treatment course accurately represents current practice. If patients fail treatment with either boceprevir or telaprevir, it is not recommended that they be re-treated with a regime containing the alternative protease inhibitor (26).
- The model does not allow for re-infection. Published outcome data in Irish patients infected with HCV suggests re-infection rates are very low in this population (89). Lower treatment efficacy estimates are applied in one-way sensitivity analysis to assess the effect of re-infection on cost-effectiveness ratios
- The model assumes that clinical effectiveness will be similar to clinical trial efficacy. A HCV treatment registry was established in Ireland at the time of re-imbursement of

the HCV protease inhibitors. It is hoped to compare the cost-utility of HCV treatment using effectiveness data from the registry once it becomes available

### 8.3.2 Application of the model for evaluation of Hepatitis C treatments in Ireland

#### *Target Population*

This model considers adult patients chronically infected with HCV Genotype 1 in Ireland. It models patients who are treatment naïve as this represents the majority of patients with HCV infection engaged in clinical care in Ireland *(Chapter 4)*. Patients can have either non-cirrhotic or cirrhotic liver disease. Patients enter the cirrhosis arms of treatment pathways in the compensated cirrhosis state as it is relatively contraindicated to treat patients with decompensated liver disease with pegylated interferon (26).

#### *Setting and Location*

The majority of HCV care in Ireland occurs through an ambulatory platform and is funded by the public health care system. Patients with more severe forms of liver disease such as decompensation, transplantation and hepatocellular carcinoma may require episodes of inpatient care and these are captured in the cost estimates reported in Chapter 5. HCV treatment occurs over 24, 28 or 48 weeks as an outpatient, the majority through hospital-based Hepatology or Infectious Disease services. Costs of HCV treatment in Ireland are borne in their entirety by the government. Pegylated interferon and ribavirin are reimbursed through the high-tech drug scheme. Telaprevir and boceprevir are hospital-only drugs and are reimbursed through the hospital budgets.

#### *Study Perspective*

This economic evaluation was conducted from the perspective of the healthcare payer in Ireland as per national Health Technology Assessment guidelines (109).

### *Treatments*

The treatments considered were the reimbursed treatment options for HCV in Ireland in August 2014. They included pegylated interferon and ribavirin dual therapy for 48 weeks (standard of care prior to 2012), and triple therapy with either telaprevir or boceprevir in addition to pegylated interferon and ribavirin. Treatment-naïve, non-cirrhotic patients with an early response to triple therapy, termed a rapid virological response, are eligible for a shortened course of treatment (24/28 weeks rather than 48 weeks). This option was included in the decision tree. The treatment regimens are complex and are presented in greater details in Chapter 2.

### *Comparators*

The option of no treatment was also considered as a comparator arm as this would be standard of care for patients who were ineligible for, or unable to tolerate an interferon-based treatment regimen and it allowed assessment of the cost-effectiveness of the current standard of care treatment.

### *Rationale for Treatments and Comparators*

The treatments and comparators chosen were the available treatment options as of August 2014. There are a number of new agents presently entering the market but the cost of these was not available at the time of the model development. Furthermore, the design of the Phase 3 clinical trials of the newer agents have frequently not contained a comparator arm which will make development of a network meta-analysis for efficacy challenging and beyond the scope of this research.

### *Treatment discontinuation*

Treatment discontinuation rates were sourced from the pivotal Phase 3 trials of boceprevir and telaprevir. In SPRINT-2, the discontinuation rate for patients on response-guided therapy with triple therapy including boceprevir was 0.23 with an average treatment duration of 15

weeks. For those patients who did not receive response-guided therapy, the discontinuation rate was 0.3 with an average treatment duration of 20 weeks (94). In ADVANCE, patients who received triple therapy including telaprevir had a discontinuation rate of 0.16 with an average exposure to telaprevir of 10.7 weeks. For those patients who did not receive response guided therapy 0.26 discontinued treatment with an average treatment duration of 36 weeks. Patients in the response guided therapy arm of ADVANCE did not have any further discontinuations after the telaprevir portion of the treatment. Patients in the placebo arm of ADVANCE, who received pegylated interferon and ribavirin alone, had a discontinuation rate of 0.44 after a mean treatment exposure of 36 weeks (188). These values were varied by +/- 20% in the deterministic sensitivity analysis.

### *Measurement of efficacy*

The efficacy of the considered agents was assessed using the network meta-analysis presented in Chapter 7. The relative efficacies for treatment-naïve patients established in that work were applied in the model. There were very few patients with cirrhosis in the clinical trials included in the meta-analysis, thus we were unable to separately assess the efficacy of the protease inhibitors in this patient cohort. The efficacy of pegylated interferon and ribavirin in patients with cirrhosis was drawn from the literature. This was a report of the SVR rates of 568 patients with cirrhosis attending 26 different treatment centres in Spain. They reported an overall SVR rate of 0.3 in patients with cirrhosis treated with pegylated interferon and ribavirin and this was the value used in cirrhosis treatment arms (205). This baseline rate was then multiplied by the relative efficacy of telaprevir and boceprevir to give estimates of the relevant treatment efficacy in cirrhosis. Treatment efficacy probabilities are displayed in Table 8-1.

**Table 8-1 Treatment efficacy probabilities in Non-cirrhotic and Cirrhotic arms**

| Parameter | Value | 95%CI | Distribution |
|---|---|---|---|
| Probability of SVR in non-cirrhotic | 0.41 | 0.4,0.42 | Beta |
| Probability of SVR in cirrhosis | 0.3 | 0.25,0.35 | Beta |
| Relative efficacy of Telaprevir | 1.69 | 1.58,1.78 | Log Normal |
| Relative efficacy of Boceprevir | 1.66 | 1.55,1.75 | Log Normal |
| Probability of SVR with Telaprevir (no cirrhosis) | 0.69 | 0.63,0.72 | n/a |
| Probability of SVR with Telaprevir (cirrhosis) | 0.51 | 0.39,0.62 | n/a |
| Probability of SVR with Boceprevir (no cirrhosis) | 0.68 | 0.65,0.73 | n/a |
| Probability of SVR with Boceprevir (cirrhosis) | 0.50 | 0.39,0.73 | n/a |

### *Time Horizon and Discount Rate*

Patients enter the model with a starting age of 41 years which is based on the PCRS treatment data presented in Chapter 4. The starting age is varied between 25 and 55 years in the deterministic sensitivity analysis. The model is run with annual cycles. The Time Horizon in the base-case scenario is 50 years to model an expected life-time. This is varied in the deterministic sensitivity analysis between 20 years and 60 years. Costs and HRQOL are discounted at a rate of 5% per annum as per current guidelines from the Department of Finance in Ireland (115). This is adjusted in the deterministic sensitivity analysis between 0% and 10%. Half-cycle correction is applied to costs and QALYs accrued during the course of the model.

### *Measurement and Valuation of preference based outcomes*

The EQ-5D 5-Level questionnaire was used to produce utility estimates in Irish patients presenting with different stages of HCV-related liver disease as presented in Chapter 6. A utility decrement associated with HCV treatment is assumed. The NICE technology appraisal group suggested a decrement of 12% for the duration of treatment with pegylated interferon and ribavirin. The addition of telaprevir or boceprevir results in a further reduction in HRQOL. The suggested adjustment by NICE was 14% for telaprevir and 13% for boceprevir (143). These decrements were applied in the treatment arms of the model and adjusted for discontinuation rates where appropriate. The development of anaemia during the course of HCV treatment also has a significant effect on the HRQOL of patients. This was estimated at 12% by Del Rio et al in their assessment of the cost-effectiveness of the use of synthetic haematological growth factors in the setting of HCV treatment (206). This further decrement has been applied to patients entering the anaemia arms of the model. The utility values used in the model are presented in Table 8-2.

**Table 8-2 Health state Utility values with 95% Confidence Intervals and Probabilistic distributions**

Source: Chapter 6

| Health state | Utility | 95% CI | Distribution |
|---|---|---|---|
| Mild | 0.75 | 0.71,0.79 | Beta |
| Moderate | 0.74 | 0.68,0.8 | Beta |
| Compensated cirrhosis | 0.64 | 0.52,0.76 | Beta |
| Decompensated cirrhosis | 0.46 | 0.21,0.7 | Beta |
| Hepatocellular carcinoma | 0.52 | 0.24,0.81 | Beta |
| Transplant Year 1 | 0.49 | 0.24,0.75 | Beta |
| Transplant after Year 1 | 0.59 | 0.52,0.67 | Beta |
| Sustained Virological Response | 0.81 | 0.75,0.87 | Beta |

### *Estimating resources and costs*

The cost of providing clinical care to patients with HCV in Ireland was derived from the micro-costing study presented in Chapter 5. The results of that study were applied as inputs in this model. The drug costs of pegylated interferon and ribavirin were sourced from the cost to the PCRS adjusted for dispensing fees and wholesale discounts as per guidelines (115). The cost of a course of telaprevir and boceprevir was calculated from the list price of these agents in Ireland (207, 208). The cost of managing adverse events in the setting of HCV treatment was established from the study of patients treated between 2001 and 2012 and presented in Chapter 4. The average cost of a course of erythropoietin was applied to the "anaemia" arms

of the model and adjusted for the probability of erythropoietin prescribing in the event of anaemia during HCV treatment in the Irish setting between 2001 and 2012. There was an additional 3 outpatient visits added to the costs in this arm, based on expert opinion on the likely requirement for extra monitoring while anaemic. The probability of developing anaemia in each treatment arm was based on a weighted average of the development of anaemia reported from the arms of the clinical trials included in the network meta-analysis in Chapter 7. There was no additional cost added for the development of depression while on HCV treatment as this was an exceptionally rare occurrence in the Phase 3 trials of boceprevir and telaprevir (94, 188).

The costs associated with monitoring while on-treatment for HCV are based on the OPD costs established by the costing study and presented in Chapter 6. The frequency of monitoring was based on clinic protocols for HCV treatment in use in the Hepatology and Infectious Diseases clinics of St. James Hospital. The costs associated with the model and the values used in the deterministic sensitivity analysis are presented in Table 8-3 and Table 8-4

**Table 8-3 Mean values of Health-state costs with 95% Confidence Intervals (CI) and probabilistic distribution**

| Healthstate | Mean Cost | 95% CI | Distribution |
|---|---|---|---|
| Mild | €398 | €336, €482 | Gamma |
| Moderate | €417 | €335, €503 | Gamma |
| Compensated cirrhosis | €1,790 | €990, €3164 | Gamma |
| Decompensated cirrhosis | €8,303 | €3,945, €14,637 | Gamma |
| Hepatocellular carcinoma | €21,992 | €15,222, €29,467 | Gamma |
| Transplant Year 1 | €137,176 | €136,024, €138,306 | Gamma |
| Transplant after Year 1 | €5,337 | €4942, €5799 | Gamma |
| Sustained Virological Response | €83 | €66, €101 | Gamma |

**Table 8-4 Cost Inputs for Drugs and on-treatment monitoring**

| Parameter | Cost | + 20% | -20% |
|---|---|---|---|
| Cost of telaprevir | €26,334 | €21,067 | €31,600 |
| Cost of boceprevir (24 weeks) | €19,333 | €15,466 | €23,200 |
| Cost of boceprevir (32 weeks) | €25,777 | €20,622 | 30,933 |
| Cost of boceprevir (44 weeks) | €35,444 | €28,355 | €42,533 |
| Cost of Peg +RBV (24 weeks) | €7,773 | €6219 | €9,328 |
| Cost of Peg +RBV (28 weeks) | €9,096 | €7,255 | €10,883 |
| Cost of Peg and RBV (48 weeks) | €15,547 | €12,438 | €18,657 |
| On-treatment monitoring (24 weeks) | €2738 | €2462 | €3,011 |
| On-treatment monitoring (28 weeks) | €2916 | €2,624 | €3,207 |
| On treatment monitoring (48 weeks) | €3856 | €3,470 | €4,241 |
| Cost of Post-treatment monitoring | €708 | €566 | €805 |
| Cost of course of erythropoietin | €4,728 | €4,149 | €5,307 |
| Cost of baseline HCV workup | €1,523 | €1,448 | €1,827 |

*Mortality*

Background mortality was derived from the Irish life-tables published by the Central Statistics Office (209). A blend of male and female life tables, based on a gender split of 70:30 was used. This gender split was informed by the epidemiology of treated patients between 2001-2012 in Ireland, presented in Chapter 4.

The 5-year survival of Irish patients with HCC was sourced from the National Cancer Registry of Ireland. This was used to develop transition probabilities from the HCC year 1 Healthstate to HCC Year 2-5. (1-probability of death) from HCC Year 1 was used as the transition probability to HCC Year 2-5. The HCC year 2-5 health-state is a tunnel state with the transition probability dependent on the years in the healthstate and based on the NCRI data. There were no further

deaths from HCC after 5 years in the NCRI data and therefore patients in HCC Yr 5 die at the background mortality rate (40).

Survival post-liver transplantation in Ireland was sourced from the National Liver Transplant Centre at St. Vincent's University Hospital (204). The survival rate for patients in the first year post-transplant was used as the transition between the transplant health-state and the post-transplant health-state. Patients with HCV do less well post-transplantation than patients without HCV and the appropriate rate was used for survival in the HCV-free versus HCV-infected arms of the model.

### *Transition Probabilities*

The Natural History Markov is similar in structure to that developed by Wright et al to assess the cost-effectiveness of treatment for mild HCV with pegylated interferon and ribavirin in the UK (160). This was published in 2006 and has been used as the basis for a number of models since. During the course of that health technology assessment, transition probabilities for patients with mild HCV were derived from a cohort of 430 patients attending the liver clinic at St. Mary's Hospital, London between 1990 and 2001. The annual state transition probabilities were calculated using modelling performed by the Medical Research Council Biostatistics Unit. For patients with more advanced liver disease, Wright et al used transition probabilities derived from a paper by Fattovich et al, which reported the natural history outcomes of 384 patients with cirrhosis attending 7 centres across Europe (146). Given the similarity in model structure between the Irish and UK models, it was felt to be valid to use the annual transition probabilities presented in the UK Mild HTA.

There were some transitions that were not included in the Wright et al model, that were possibilities in the Irish model. In this model it is possible to transition from HCC year 1 to Transplantation. Irish data from the National Liver Transplant Unit on transplantation of patients infected with HCV who developed HCC between 1997 and 2009 was sought (210). A weighted average of the rate of transplantation in this setting was derived to inform the

transition probability. As described in the 8.3.2.12 above, national data on 5-year survival post-transplantation and post-HCC were sourced from the National Liver Transplant Unit and the National Cancer Registry to inform the transitions from Transplant to Post transplant and the transitions between the HCC disease states (40, 204).

In addition, successful treatment of HCV results in reduced rates of decompensation and HCC development in patients with advanced liver disease (203). Patients with cirrhosis who attain a SVR are at reduced risk of developing these late complications. Therefore, the transition probabilities from compensated cirrhosis to decompensated cirrhosis and from the cirrhosis states to HCC are decreased for patients who achieve an SVR, in order to reflect this decreased risk (relative risk of decompensation post-SVR 0.12 (95%CI 0.06, 0.24)and relative risk of HCC post-SVR 0.27 (95%CI 0.21, 0.36)) (203). The annual transition probabilities are presented in Table 8-5.

**Table 8-5 Transition Probability Matrix**

| Healthstate | Mild | Mod | Comp. Cirrhosis | Decomp. Cirrhosis | HCC Yr 1 | HCC Yr 2-5 | HCC Yr 5 | OLT YR 1 | OLT > YR1 | Death |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mild** | # | 0.025$^{\$}$ | | | | | | | | CSO |
| **Moderate** | | # | 0.037$^{\$}$ | | | | | | | CSO |
| **Comp. Cirrhosis** | | | # | 0.039$^{\$}$ | 0.014$^{\$}$ | | | 0.02$^{\$}$ | | CSO |
| **Decomp Cirrhosis** | | | | # | 0.014$^{\$}$ | | | 0.02$^{\$}$ | | 0.13$^{\$}$ |
| **HCC Yr 1** | | | | | # | | | | | 0.53 |
| **HCC Yr 2-5** | | | | | | # | | | | 0.26, 0.16, 0.11, 0.04* |
| **HCC Yr 5** | | | | | | | # | | | CSO |
| **OLT Yr 1** | | | | | | | | # | | 0.17 (HCV+) 0.14(HCV-)^ |
| **OLT > YR 1** | | | | | | | | | # | 0.07 (HCV+) 0.02 (HCV-) |

*Abbreviations: Mod = Moderate; Comp. = Compensated; Decomp = Decompensated; HCC = Hepatocellular Carcinoma; YR = year; OLT = Orthotopic Liver Transplantation; HCV + = Hepatitis C positive; HCV - = Hepatitis C negative; #= (1-Sum of other probabilities in the row); CSO = Central Statistics Office Life Tables, *Tunnel State - Yearly probabilities with progression through 4 years (NCRI) ^SVUH transplant survival data $ Wright et al*

*Analysis of Results*

The model examines the expected lifetime costs and QALY gains of the considered treatments under the baseline scenario consisting of a population of 80% non-cirrhotic and 20% cirrhotic HCV patients. The model was run through a thousand random iterations, using distributions of values rather than point estimates, in order to accurately represent the uncertainty around the variables. The distributions chosen were those most likely to fit the nature of the data. Gamma distributions were used for costs to account for the positive skew likely in cost parameters. The log normal distribution was used for relative risks to reflect the ratio nature of these parameters, and the Beta distribution was used for probabilities and utilities as these are bounded between 0 and 1. A fully incremental analysis was performed and results are summarised as probabilistic Incremental Cost Effectiveness Ratios or ICERs and graphically represented on a cost-effectiveness plane. Deterministic results were determined using point estimates for the variables to produce a fully incremental analysis with the deterministic ICERs presented alongside the probabilistic ones for comparison.

The uncertainty surrounding the decision on the cost-effectiveness of the treatments is presented with scatterplots of the incremental costs and effectiveness of the treatments and also with a cost-effectiveness acceptability curve (CEAC). The CEAC displays the probability that a treatment is cost-effective over a range of WTP thresholds, given the data (126). Each treatment considered is represented by a separate line on the graph. Ellipses with 95% CI and willingness-to-pay thresholds of two-way comparisons of treatment strategies are also presented. The threshold is currently €45,000/QALY in Ireland.

Deterministic one-way sensitivity analysis (DSA) was performed on all variables using upper and lower bounds that covered realistic scenarios. A Tornado diagram considering all strategies from their net benefit perspective is presented to demonstrate the variables that produced the most significant changes in the model on one-way sensitivity testing. Changes in

ICERs that would change the decision are presented in the Results. The analysis in full is available in the Appendix 4. Tornado diagrams and ICERs of two-way comparisons are also presented.

In separate scenario analyses, the model was re-run to examine the impact of having a 100% non-cirrhotic cohort and 100% cirrhotic cohort. The results are presented in a similar format to the baseline population results.

### *Model Validation*

Response to predictable manipulations of the model, such as setting all parameters to zero or making drug costs and efficacy equivalent was examined in order to validate the model. The survival of patients in the natural history arm of the model was compared to the survival of patients in a model of background mortality alone to test whether there was a disease-related mortality evident in the HCV model.

## 8.4 Results

### 8.4.1 Base case population

In the basecase scenario, boceprevir would be considered the most cost-effective option under current WTP thresholds with an ICER of €34,210. None of the treatment strategies are dominated in the analysis, although the ICER generated for telaprevir would be above the current willingness to pay (WTP) threshold. The cost, efficacy and ICERs produced by the PSA are summarised in Table 8-6. The cost, efficacy and ICER produced by the DSA are summarised in Table 8-7. Figure 8-6 displays the incremental cost versus effectiveness on the cost-effectiveness plane.

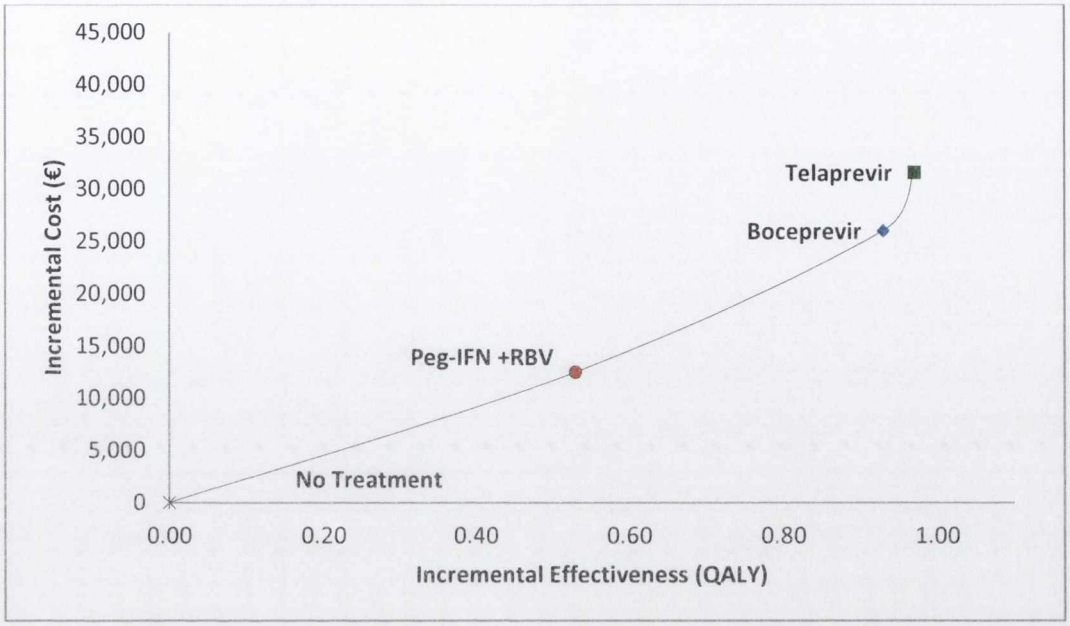



**Figure 8-6 PSA Incremental Cost-effectiveness plane for all treatment strategies**

**Table 8-6 Summary of Life-time Costs, QALY, and cost-effectiveness ratios produced by the Probabilistic Analysis**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Probabilistic) |
|---|---|---|---|---|---|
| No Treatment | €24,017 | 11.33 | | | |
| Peg-IFN + RBV | €36,483 | 11.86 | €12,485 | 0.53 | €23,383 |
| Boceprevir | €49,998 | 12.26 | €13,515 | 0.40 | €34,210 |
| Telaprevir | €55,561 | 12.30 | €5,562 | 0.04 | €135,482 |
| Telaprevir vs Peg-IFN +RBV | | | €19,077 | 0.44 | €43,744 |

**Table 8-7 Summary of Life-time Costs, QALY, and cost-effectiveness ratios produced by the deterministic analysis**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Deterministic) |
|---|---|---|---|---|---|
| No Treatment | €23,660 | 11.63 | | | |
| Peg-IFN + RBV | €36,686 | 12.26 | €13,025 | 0.63 | €20,532 |
| Boceprevir | €48,109 | 12.73 | €11,422 | 0.47 | €24,233 |
| Telaprevir | €55,159 | 12.79 | €7,050 | 0.06 | €128,082 |

*Analysis of Decision Uncertainty*

The probability of which strategy is the most cost-effective varies according to the WTP threshold considered, as shown in the CEAC in Figure 8-7. At the current WTP threshold of €45,000/QALY, boceprevir has the greatest probability of being cost-effective.

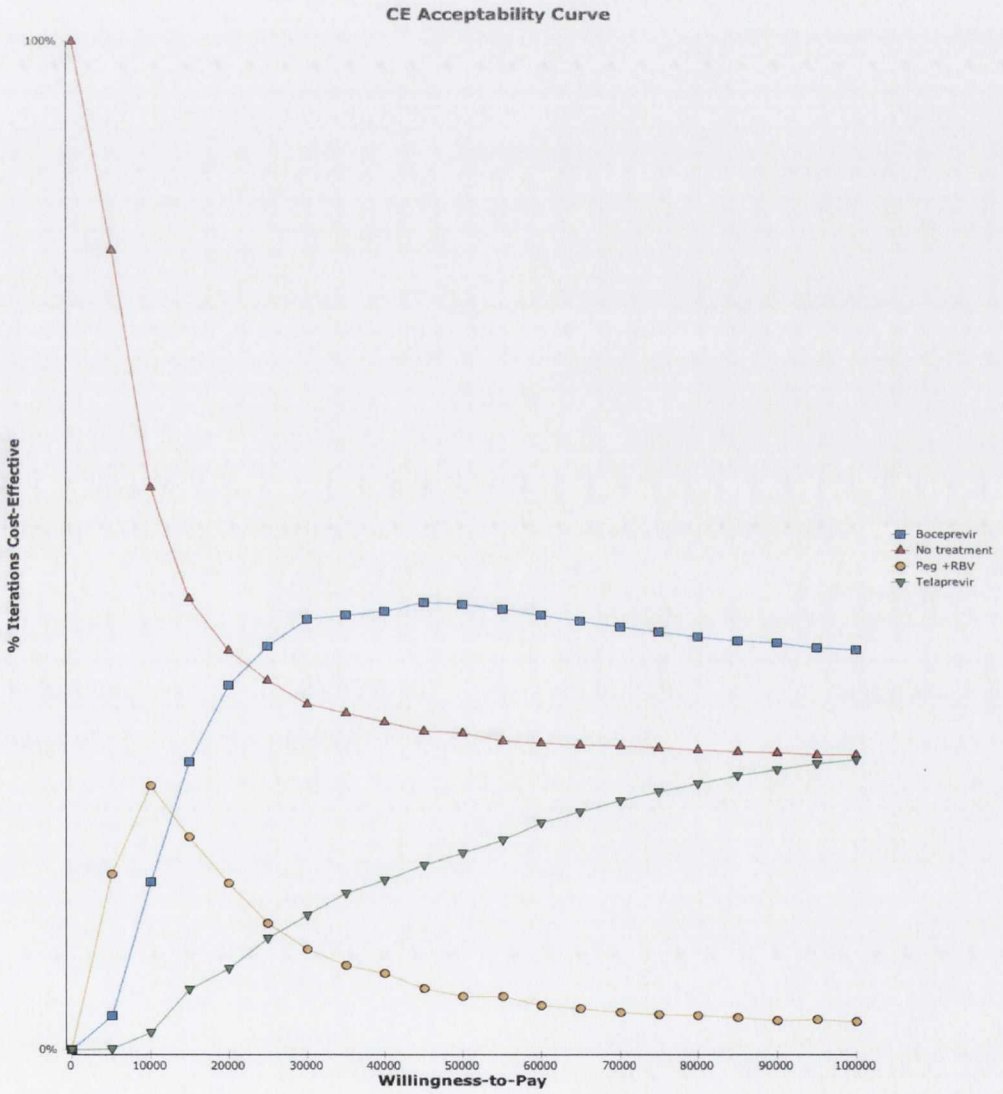



**Figure 8-7 Cost-effectiveness acceptability curve of considered treatment strategies in the baseline population**

Figure 8-8 displays a scatterplot of the incremental cost-effectiveness of the treatment strategies. This is further evaluated using 95% ellipses of pair-wise incremental comparisons in Figures 8-9 to 8-11.

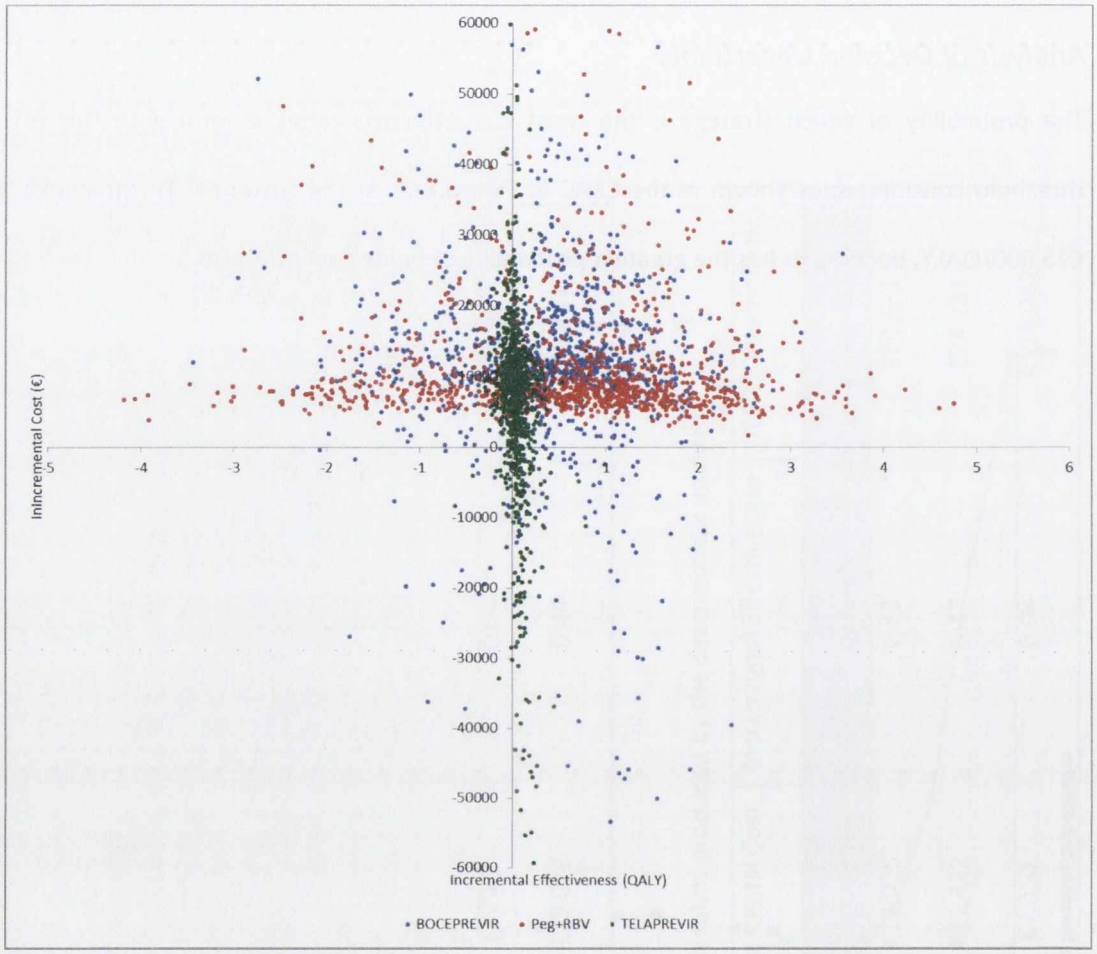



**Figure 8-8 Scatterplot of incremental lifetime Costs versus QALYs in the baseline population**

*(Peg-IFN+RBV incremental to No Treatment, Boceprevir incremental to Peg-IFN +RBV, Telaprevir incremental to Boceprevir)*

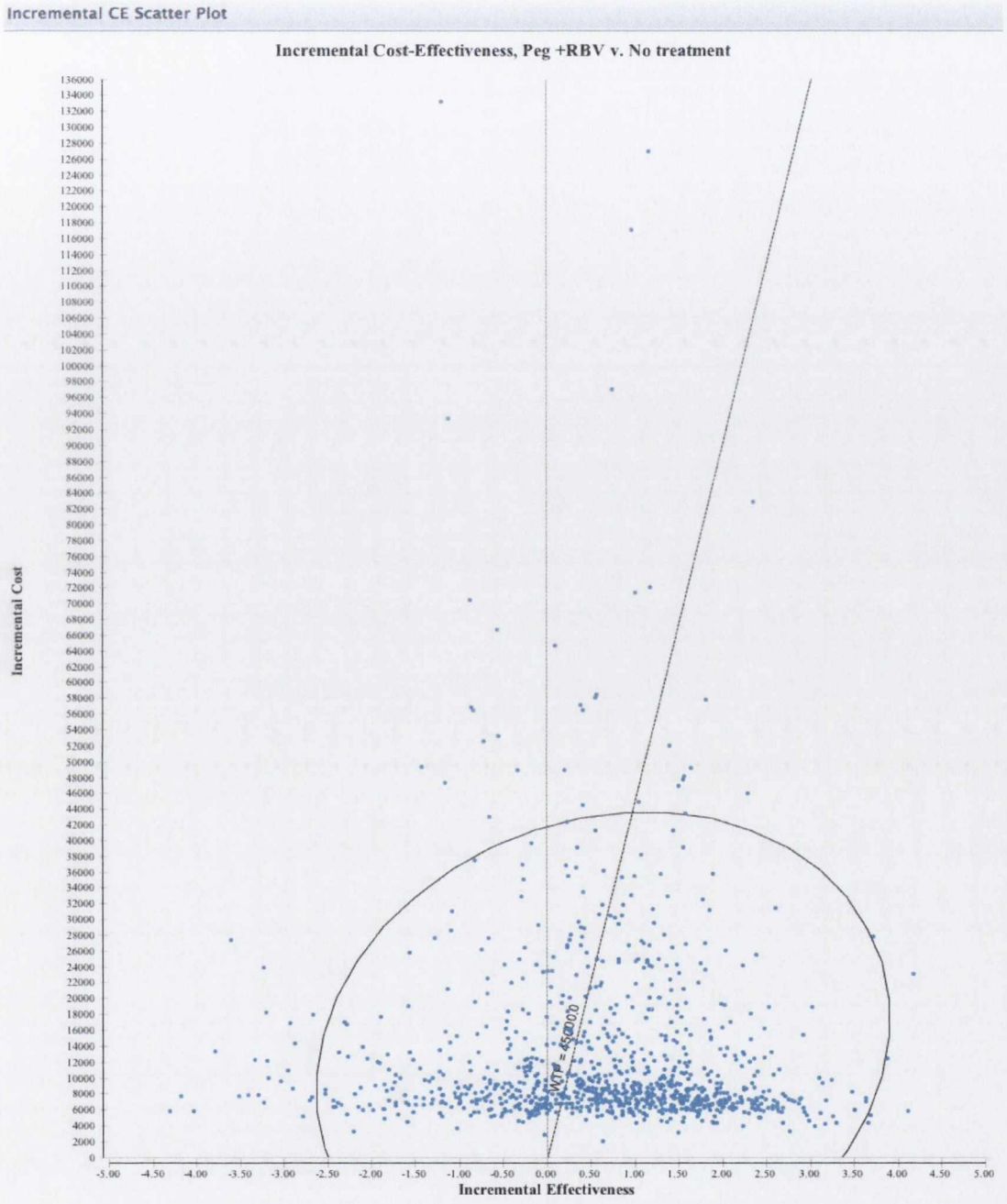



**Figure 8-9 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Peg-IFN+RBV versus No treatment in the baseline population**

The ellipse in Figure 8-9 demonstrates that at a willingness to pay threshold of €45,000, 64% of the iterations of the PSA would find Peg-IFN and RBV a cost-effective option when compared to No treatment.

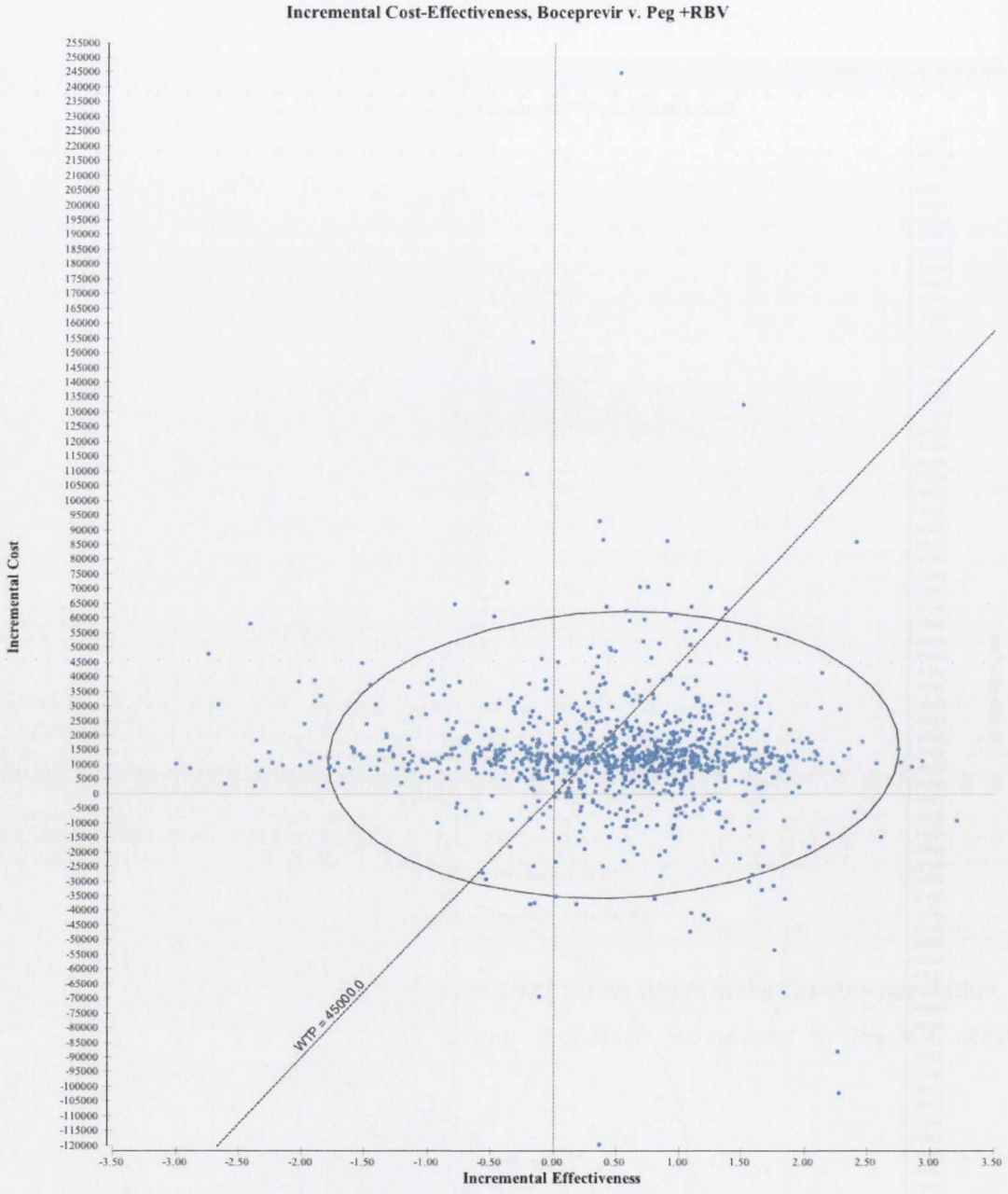



**Figure 8-10 Scatterplot ellipse demonstrating 95% CI and WTP threshold of BOC versus Peg-IFN+RBV in the baseline population**

The ellipse in Figure 8-10 demonstrates that at a willingness to pay threshold of €45,000, 61% of the iterations of the PSA would find Boceprevir a cost-effective option when compared to Peg and RBV. In 51% of the iterations, BOC was more costly, but more effective than PEG+RBV with an ICER under the WTP threshold (Quadrant 1) and in 10% it was less costly and more effective (Quadrant 2)

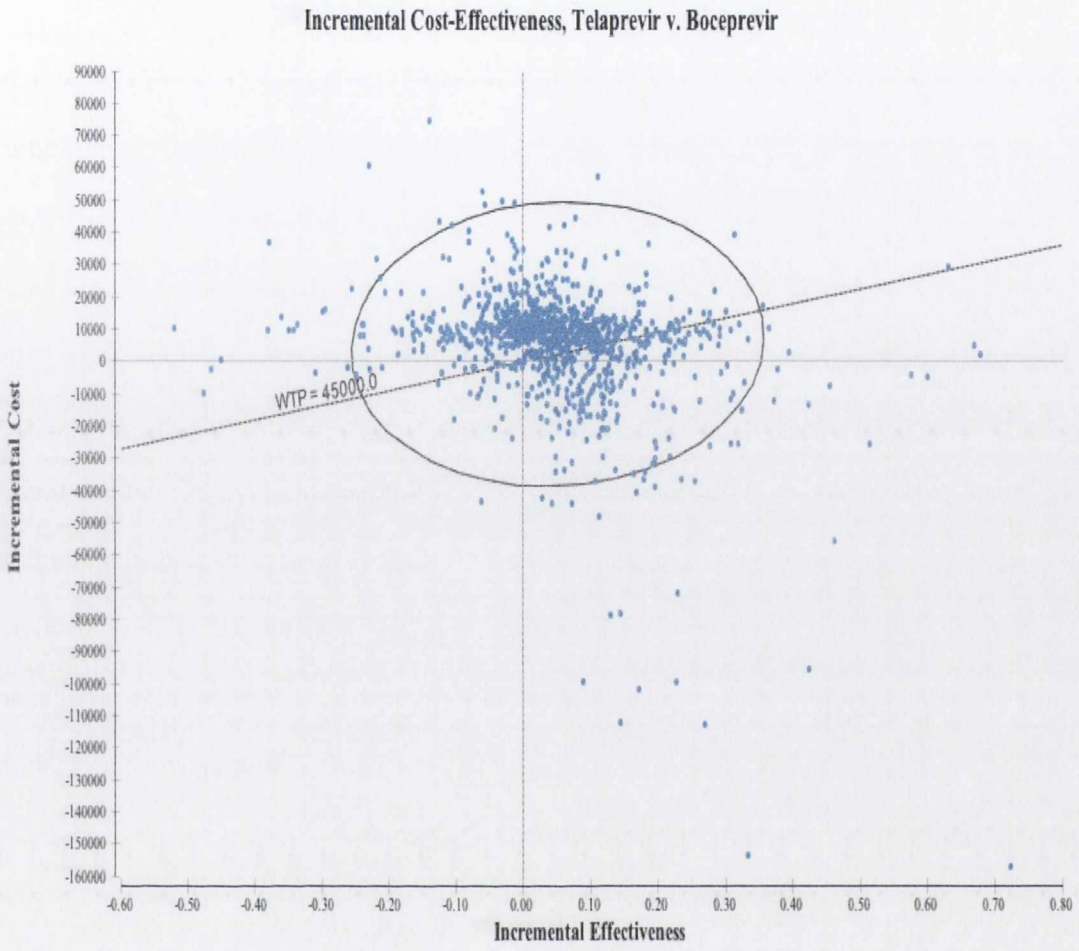



**Figure 8-11 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Telaprevir versus Boceprevir in the baseline population**

The ellipse in Figure 8-11 demonstrates that at a willingness to pay threshold of €45,000, 25% of the iterations of the PSA would find Telaprevir a cost-effective option when compared to Boceprevir. In 9% of the iterations, Telaprevir was more costly but more effective than boceprevir with an ICER below €45,000. In 16% of the iterations Telaprevir was less costly and more effective than Boceprevir (Quadrant 2). The majority of the iterations (46%) found telaprevir to be more costly and more effective than boceprevir with an ICER >€45,000. In 26% of the iterations, Telaprevir fell in Quadrant 4 being more costly and less effective than Boceprevir.

### *Deterministic Sensitivity Analysis*

Under deterministic sensitivity analysis of all the considered strategies, the model proved to be sensitive to five variables. The model was sensitive to the discount rate applied, the proportion of the patients with cirrhosis on entering the model, the time horizon of the model and the starting age of patients entering the model along with the utility value for SVR (Figure 8-12). Adjustment of the relative efficacies of boceprevir and telaprevir resulted in telaprevir being dominated under some scenarios. Decreasing the Time horizon to 20 years from a basecase of 50 meant that the ICER for Boceprevir versus PEG and RBV approached, but did not breach €45,000. (Table 8-8) If only telaprevir versus boceprevir were considered, reducing the drug cost of telaprevir by 20% brought the ICER below €45,000 (€34,064). In all other scenarios considered the ICER for telaprevir remained above the threshold in this basecase population. Full results of the one-way sensitivity analysis along with Tornado diagrams of the ICERS of pairwise comparisons are displayed in Supplemental Appendix 4.

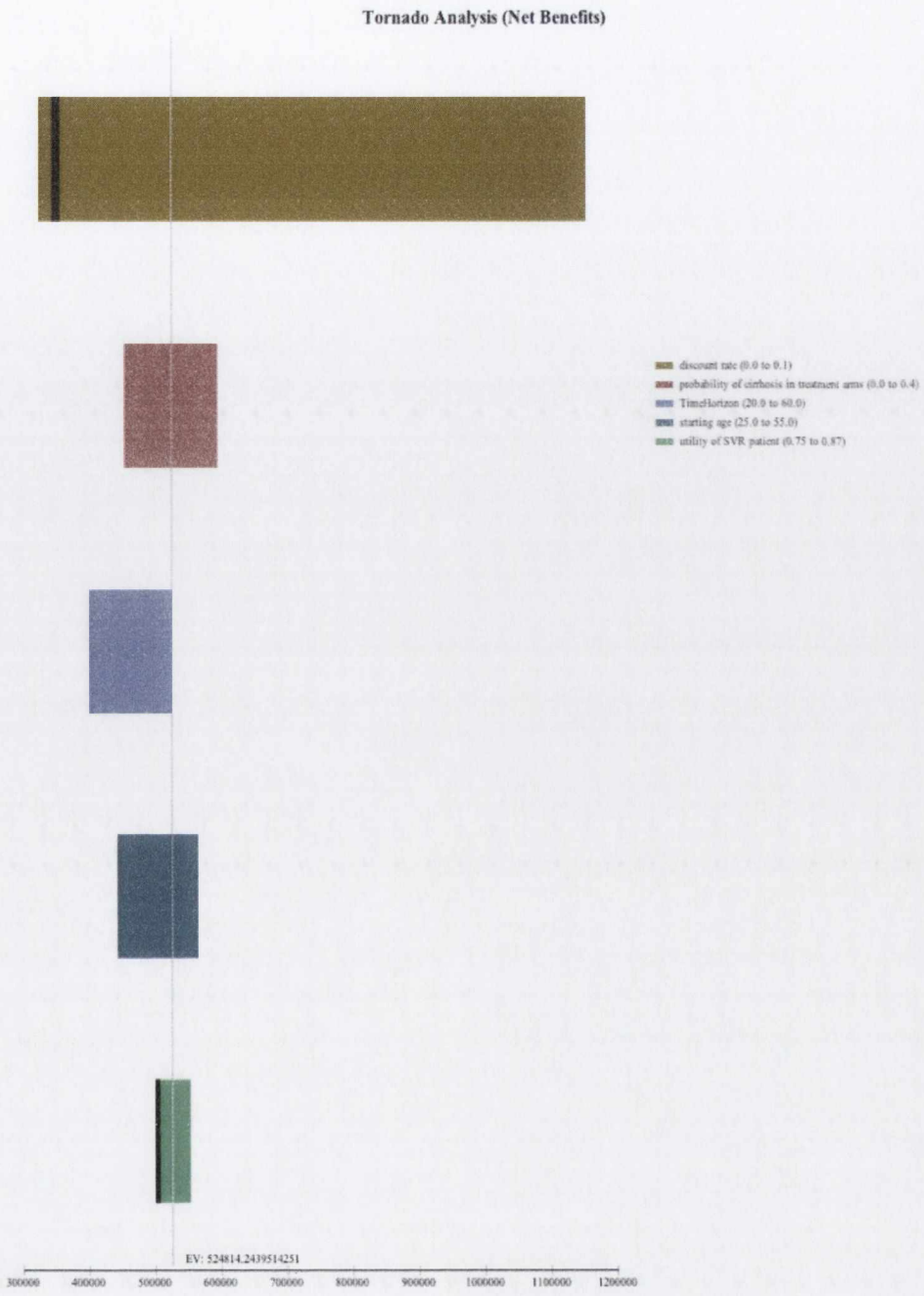



**Figure 8-12 Tornado diagram displaying variables that model is sensitive to in the baseline population**

**Table 8-8 Results of Deterministic sensitivity analysis of model including all treatment strategies**

| Variable | Basecase Value | Low Value | High Value | Strategy | Basecase ICER | Low ICER | High ICER |
|---|---|---|---|---|---|---|---|
| **Discount Rate** | 0.05 | 0.0 | 0.1 | NT | 0 | 0 | 0 |
| | | | | PR | €20,533 | €2,506 | €53,998 |
| | | | | BOC | €24,234 | €4,487 | €53,925 |
| | | | | TEL | €128082 | €71,349 | €160,083 |
| **Utility of SVR** | 0.81 | 0.75 | 0.87 | NT | 0 | 0 | 0 |
| | | | | PR | €20,533 | €49,330 | €12,964 |
| | | | | BOC | €24,234 | €52,566 | €15,746 |
| | | | | TEL | €128,082 | €158,966 | €107,246 |
| **Probability of cirrhosis in treatment arms** | 0.2 | 0 | 0.4 | NT | 0 | 0 | 0 |
| | | | | PR | €20,533 | €23,070 | €20,299 |
| | | | | BOC | €24,234 | €17,045 | €23,992 |
| | | | | TEL | €128,082 | €186,230 | €77,787 |
| **Time Horizon** | 50 | 20 | 60 | NT | 0 | 0 | 0 |
| | | | | PR | €20,533 | €42,413 | €20,353 |
| | | | | BOC | €24,234 | €44,512 | €24,051 |
| | | | | TEL | €128,082 | €152,895 | €127,762 |
| **Starting Age** | 41 | 25 | 55 | NT | 0 | 0 | 0 |
| | | | | PR | €20,553 | €16,748 | €31,130 |
| | | | | BOC | €24,234 | €20,333 | €34,506 |
| | | | | TEL | €128,082 | €120,696 | €142,802 |

### 8.4.2 Comparison of Hepatitis C treatment options in a non-cirrhotic cohort

In the scenario considering only patients with mild to moderate HCV at baseline, the lifetime costs are lower than in the basecase and the QALY gains are higher for all strategies. The ICERs are similar to the basecase as the incremental costs and effects are similar to those seen in the basecase. Peg-IFN + RBV are subject to extended dominance and the ICER for telaprevir remains above current WTP thresholds. (Table 8-9) The lifetime cost, efficacy and ICERs produced by the PSA are summarised in Table 8-9. The lifetime cost, efficacy and ICERs produced by the DSA are summarised in Table 8-10. Figure 8-13 displays the mean incremental costs versus effectiveness values on the cost-effectiveness plane.

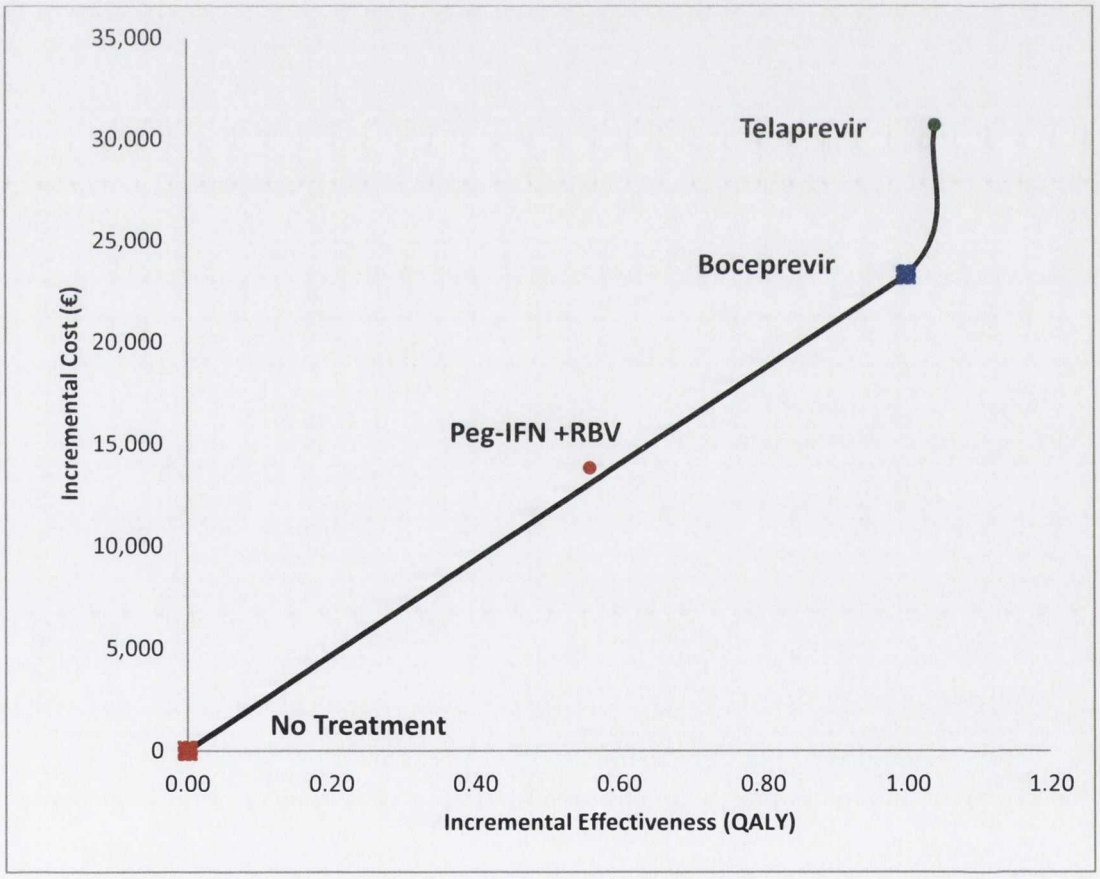



**Figure 8-13 Incremental Cost-effectiveness plane for all treatment strategies in patients without cirrhosis**

**Table 8-9 Summary of Life-time Costs, QALY, and cost-effectiveness ratios in a cohort with mild/moderate HCV at baseline using Probabilistic analysis**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Probabilistic) |
|---|---|---|---|---|---|
| No Treatment | €14,890 | 12.64 | | | |
| Peg-IFN + RBV | €28,701 | 13.20 | €13,810 | 0.56 | €24,820 (Ext. Dom.) |
| Boceprevir | €38,174 | 13.64 | €9,472 | 0.44 | €21,559 |
| Telaprevir | €45,591 | 13.68 | €7,416 | 0.04 | €167,729 |
| Telaprevir vs Peg-IFN +RBV | | | €16,889 | 0.48 | €34,924 |

**Table 8-10 Summary of Life-time Costs, QALY, and cost-effectiveness ratios in a cohort with mild/moderate HCV at baseline under Deterministic analysis**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Deterministic) |
|---|---|---|---|---|---|
| No Treatment | €14,864 | 13.10 | | | |
| Peg-IFN + RBV | €28,356 | 13.58 | €13,491 | 0.57 | €23,662 (Ext. Dom.) |
| Boceprevir | €35,951 | 14.02 | €7,595 | 0.45 | €17,045 |
| Telaprevir | €45,460 | 14.07 | €9,509 | 0.05 | €186,230 |

*Analysis of Decision Uncertainty*

At the current WTP threshold, boceprevir has the highest probability of cost-effectiveness. Figure 8-14 displays the CEAC for all treatment strategies showing the probability of cost-effectiveness of the strategies over a range of willingness to pay thresholds.

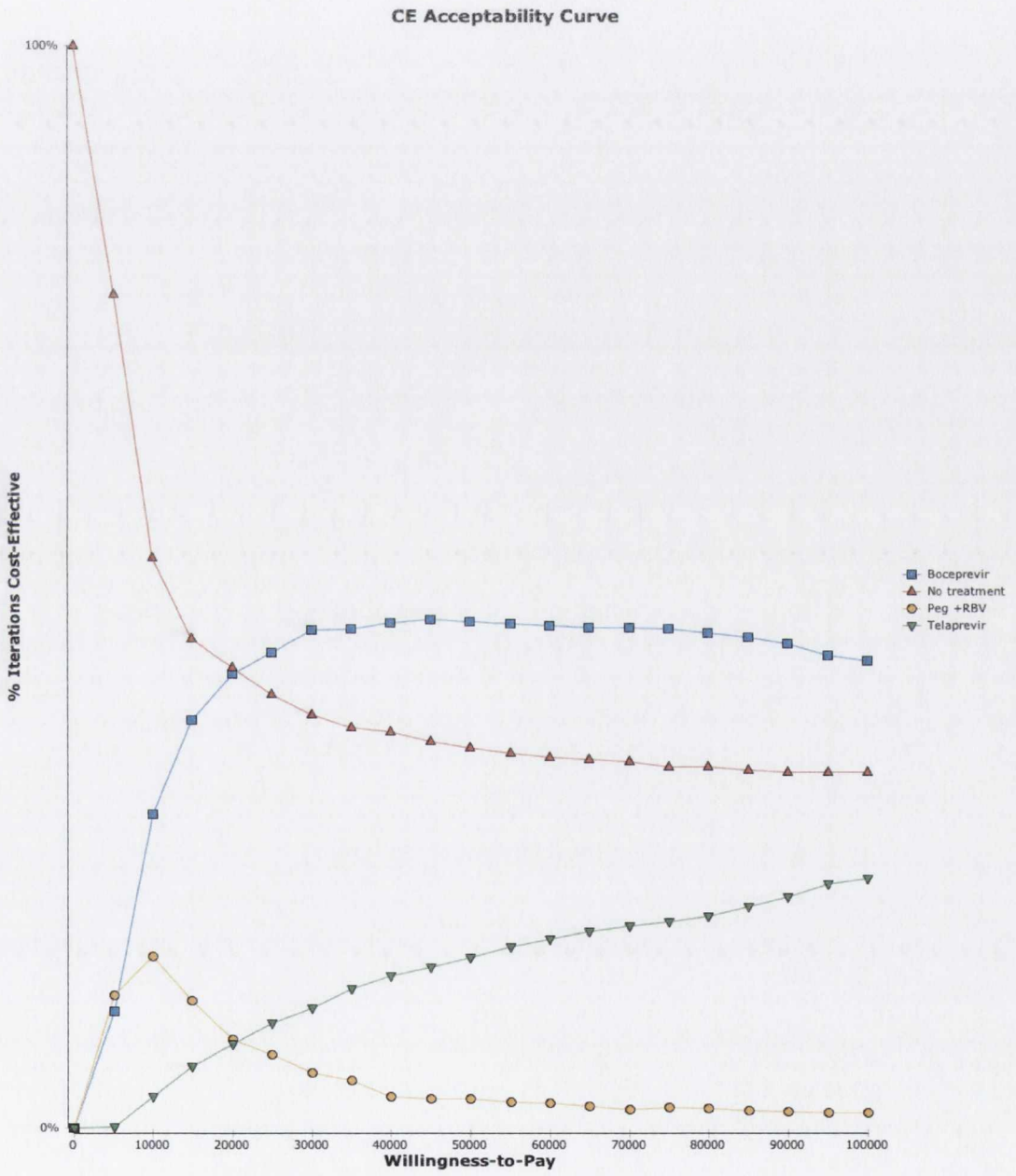



**Figure 8-14 Cost-effectiveness acceptability curve of available treatment strategies in a non-cirrhotic cohort**

Figure 8-15 displays a scatterplot of the incremental cost-effectiveness of the treatment strategies in a non-cirrhotic cohort. This is further evaluated using 95% ellipses of pair-wise incremental comparisons in Figures 8-16 to 8-18.

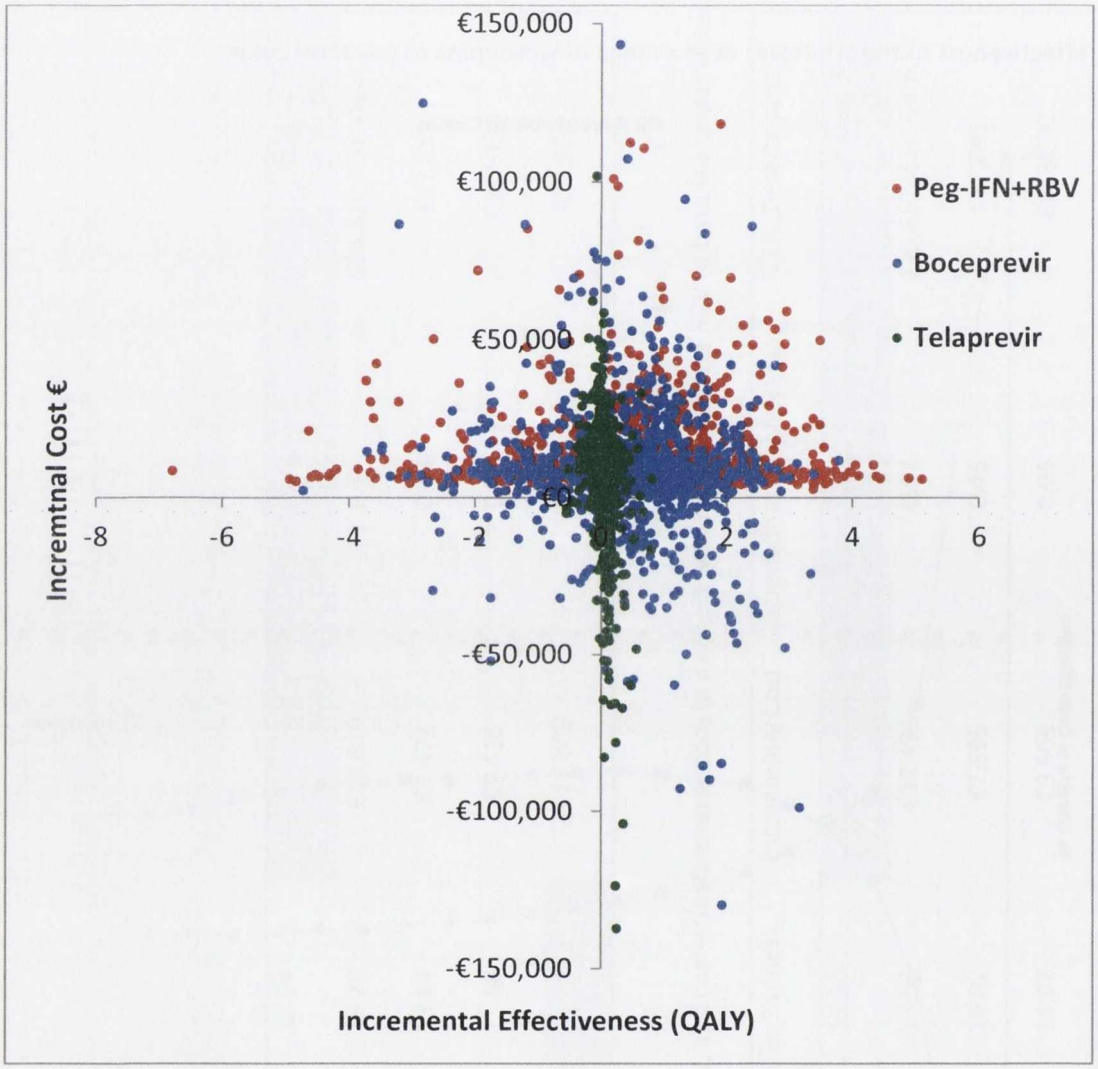



**Figure 8-15 Scatterplot of Incremental lifetime Costs versus QALYs in patients without cirrhosis**

*(Peg-IFN + RBV incremental to No Treatment, Boceprevir incremental to Peg-IFN+RBV, Telaprevir incremental to Boceprevir)*

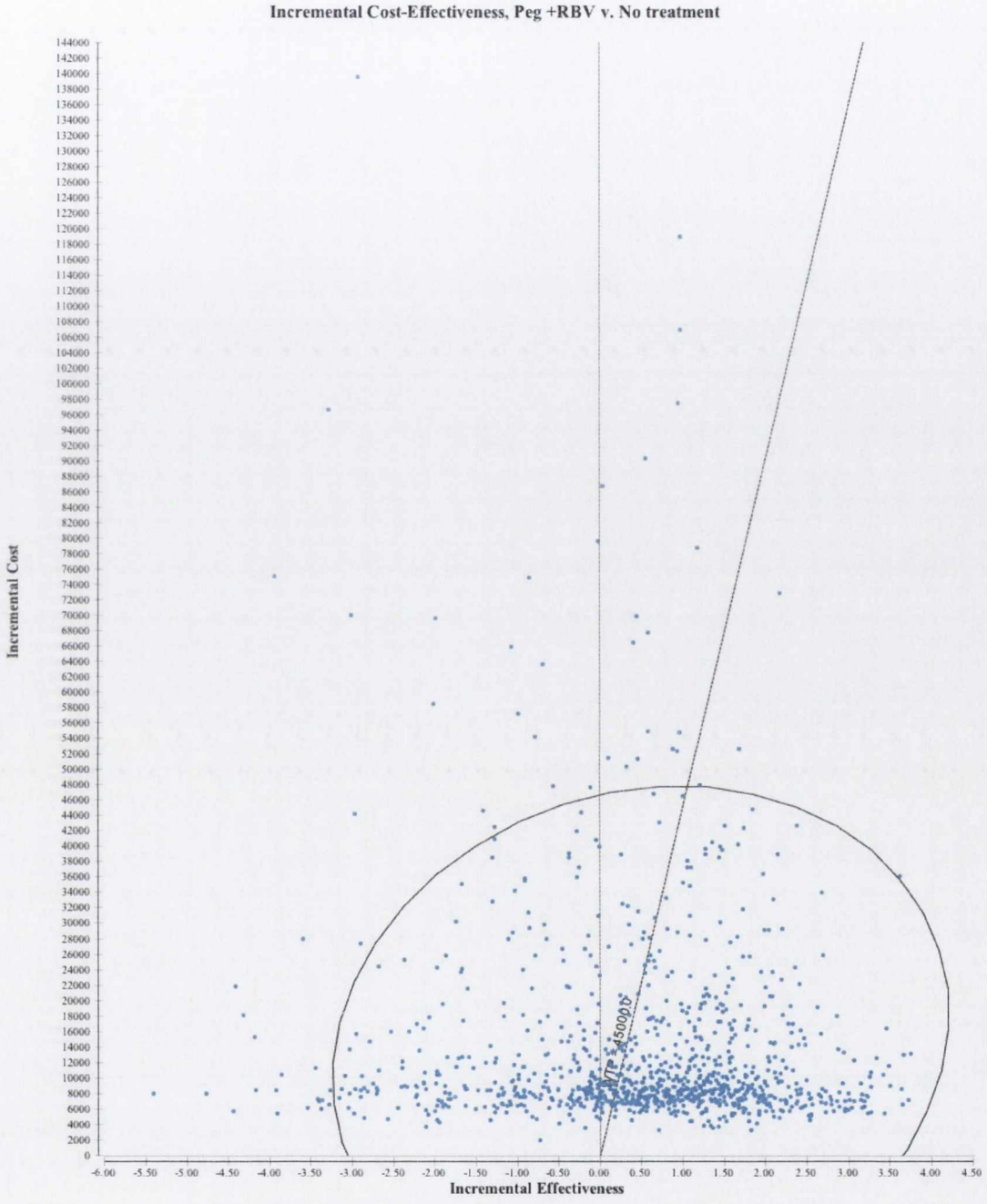



**Figure 8-16 Scatterplot ellipse showing 95% CI and WTP threshold of Peg-IFN+RBV versus No treatment in a non-cirrhotic cohort**

The ellipse in Figure 8-16 demonstrates that at a willingness to pay threshold of €45,000, 62% of the iterations of the PSA would find PEG-IFN and RBV a cost-effective option when compared to No treatment in this population with mild to moderate HCV.

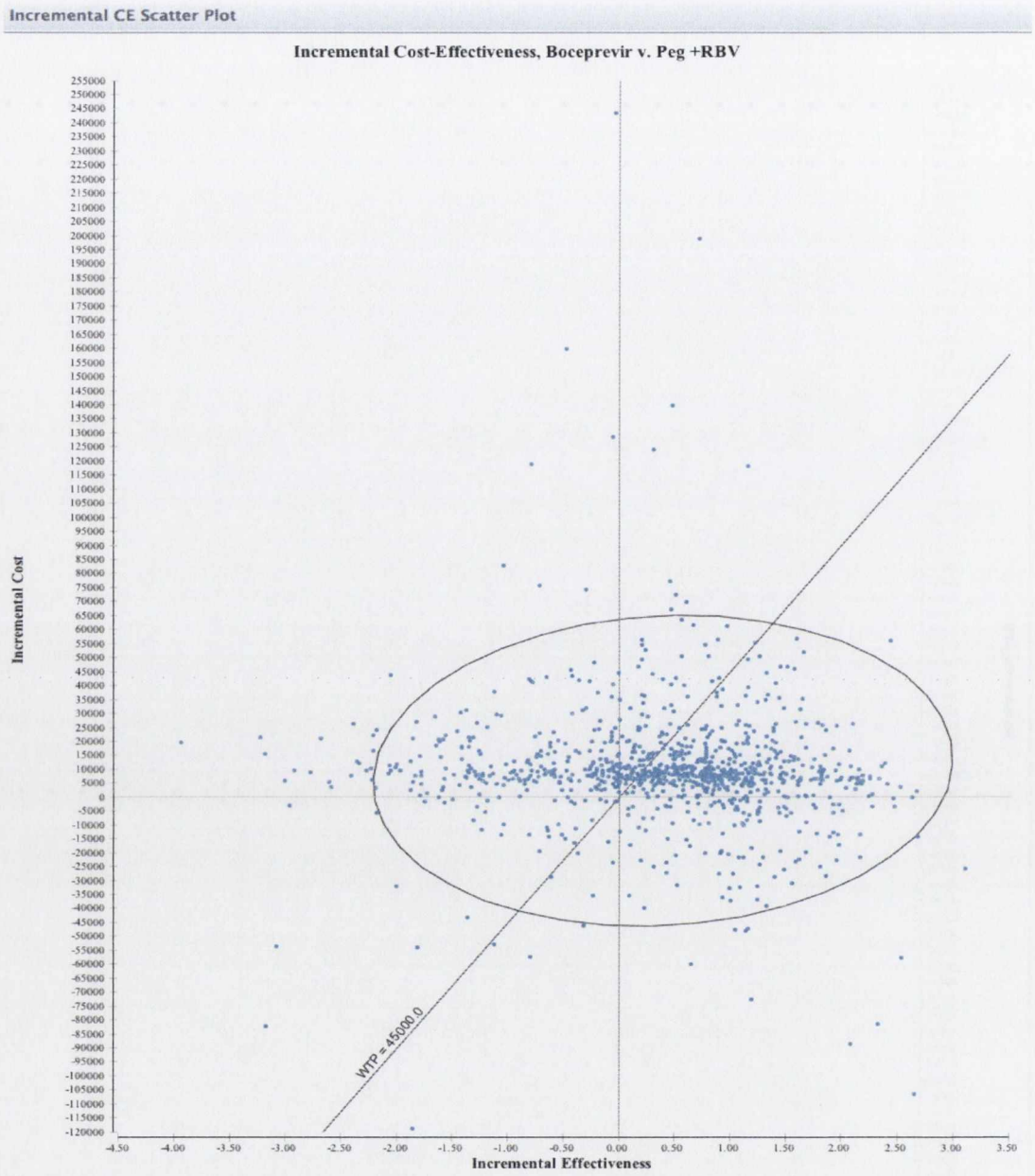



**Figure 8-17 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Boceprevir versus Peg-IFN +RBV in the non-cirrhotic cohort**

The ellipse in Figure 8-17 demonstrates that at a willingness to pay threshold of €45,000, 60% of the iterations of the PSA would find Boceprevir a cost-effective option when compared to Peg-IFN and RBV. In 47% of the iterations, BOC was more costly, but more effective than PEG+RBV with an ICER under the WTP threshold (Quadrant 1) and in 13% it was less costly and more effective (Quadrant 2).

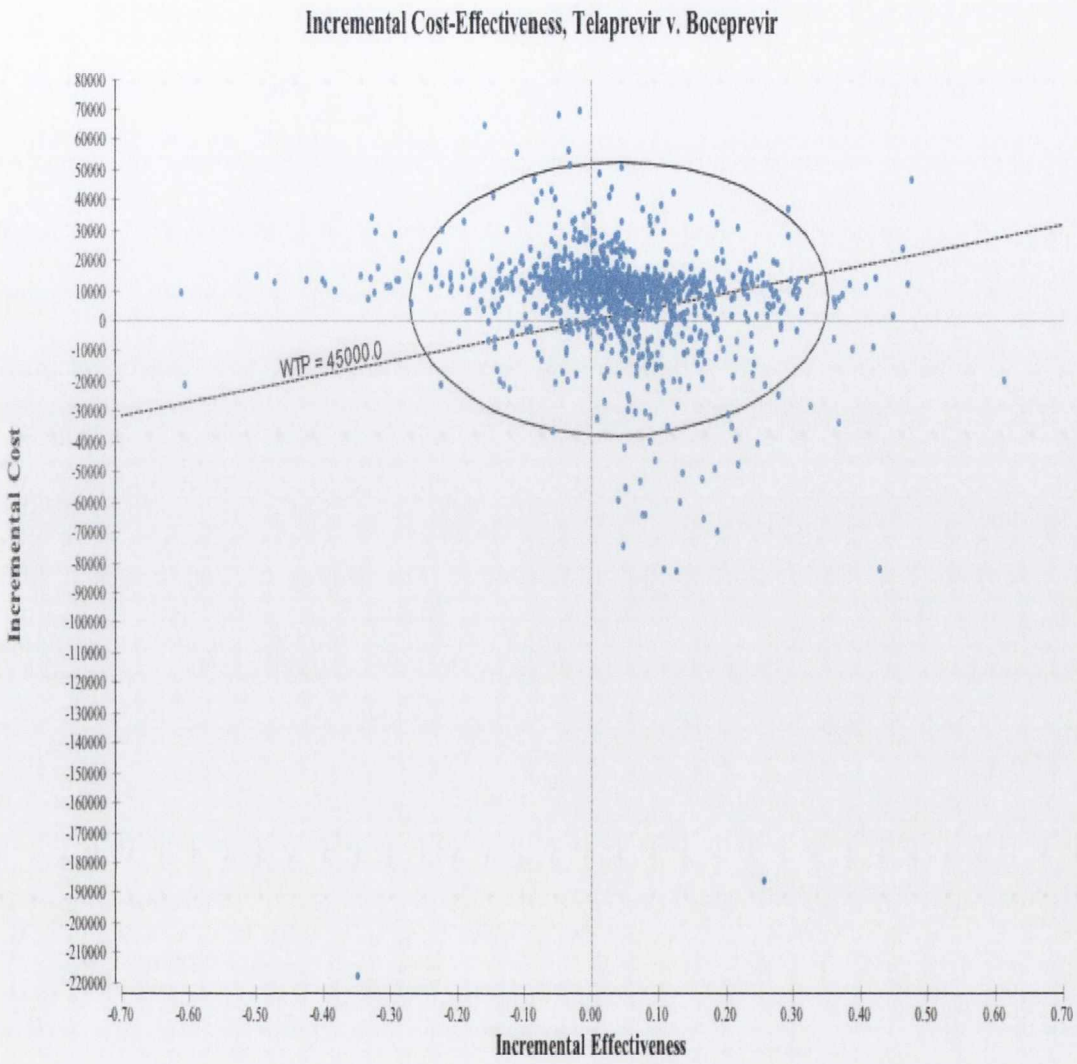



**Figure 8-18 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Telaprevir versus Boceprevir in the non-cirrhotic population**

The ellipse in Figure 8-18 demonstrates that at a willingness to pay threshold of €45,000, 34% of the iterations of the PSA would find Telaprevir a cost-effective option when compared to Boceprevir in this population. In 9% of the iterations, Telaprevir was more costly but more effective than boceprevir with an ICER below €45,000. In 16% of the iterations Telaprevir was less costly and more effective than Boceprevir (Quadrant 2). The majority of the iterations (46%) found telaprevir to be more costly and more effective than boceprevir with an ICER >€45,000. In 26% of the iterations, Telaprevir fell in Quadrant 4 being more costly and less effective than Boceprevir.

### 8.4.3 Comparison of Hepatitis C treatment options in a cirrhotic cohort

In the scenario considering only patients with cirrhosis from HCV at baseline, the cumulative lifetime costs are higher than in the basecase and the cumulative QALY gains are lower for all strategies. The ICER for Peg-IFN +RBV versus No Treatment is lower than the basecase, as the incremental effectiveness is higher and the incremental cost is lower. The ICER for Telaprevir versus Peg-IFN +RBV is higher than the basecase, but would still be considered cost-effective. Boceprevir is dominated in this scenario by Telaprevir. The lifetime cost, efficacy and ICERs produced by the PSA are summarised in Table 8-11. The lifetime cost, efficacy and ICERs produced by the DSA are summarised in Table 8-12. Figure 8-19 displays the mean incremental costs versus effectiveness values on the cost-effectiveness plane.

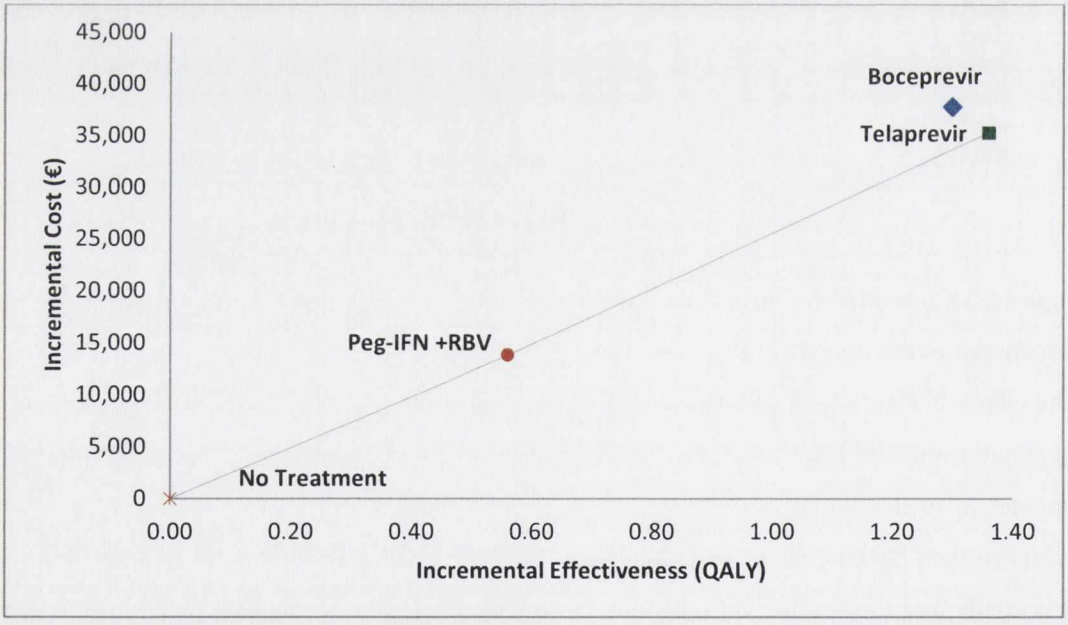



**Figure 8-19 Incremental Cost-effectiveness plane for all treatment strategies in patients with cirrhosis**

**Table 8-11 Summary of Life-time Costs, QALY, and cost-effectiveness ratios in a cohort with cirrhosis at baseline under Probabilistic conditions**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Probabilistic) |
|---|---|---|---|---|---|
| No Treatment | €61,176 | 6.09 | | | |
| Peg-IFN + RBV | €72,610 | 6.88 | €11,433 | 0.79 | €14,418 |
| Telaprevir | €96,421 | 7.45 | €23,810 | 0.57 | €41,802 |
| Boceprevir | €98,920 | 7.39 | €2,499 | -0.06 | Dominated |
| Boceprevir vs Peg-IFN +RBV | | | €26,310 | 0.51 | €51,360 |

**Table 8-12 Summary of Life-time Costs, QALY, and cost-effectiveness ratios in a cohort with cirrhosis at baseline under deterministic conditions**

| | Cost | Effectiveness | Incremental Cost | Incremental Effectiveness | ICER (Deterministic) |
|---|---|---|---|---|---|
| No Treatment | €58,845 | 6.11 | | | |
| Peg-IFN + RBV | €70,008 | 7.0 | €11,162 | 0.89 | €12,524 |
| Telaprevir | €93,957 | 7.64 | €23,949 | 0.65 | €37,108 |
| Boceprevir | €96,740 | 7.57 | €2,783 | -0.07 | Dominated |

*Analysis of Decision Uncertainty*

In this population, at the current WTP threshold, telaprevir would have the greatest probability of being cost-effective. Figure 8-20 displays the CEAC for all treatment strategies showing the probability of cost-effectiveness of the strategies over a range of WTP thresholds.

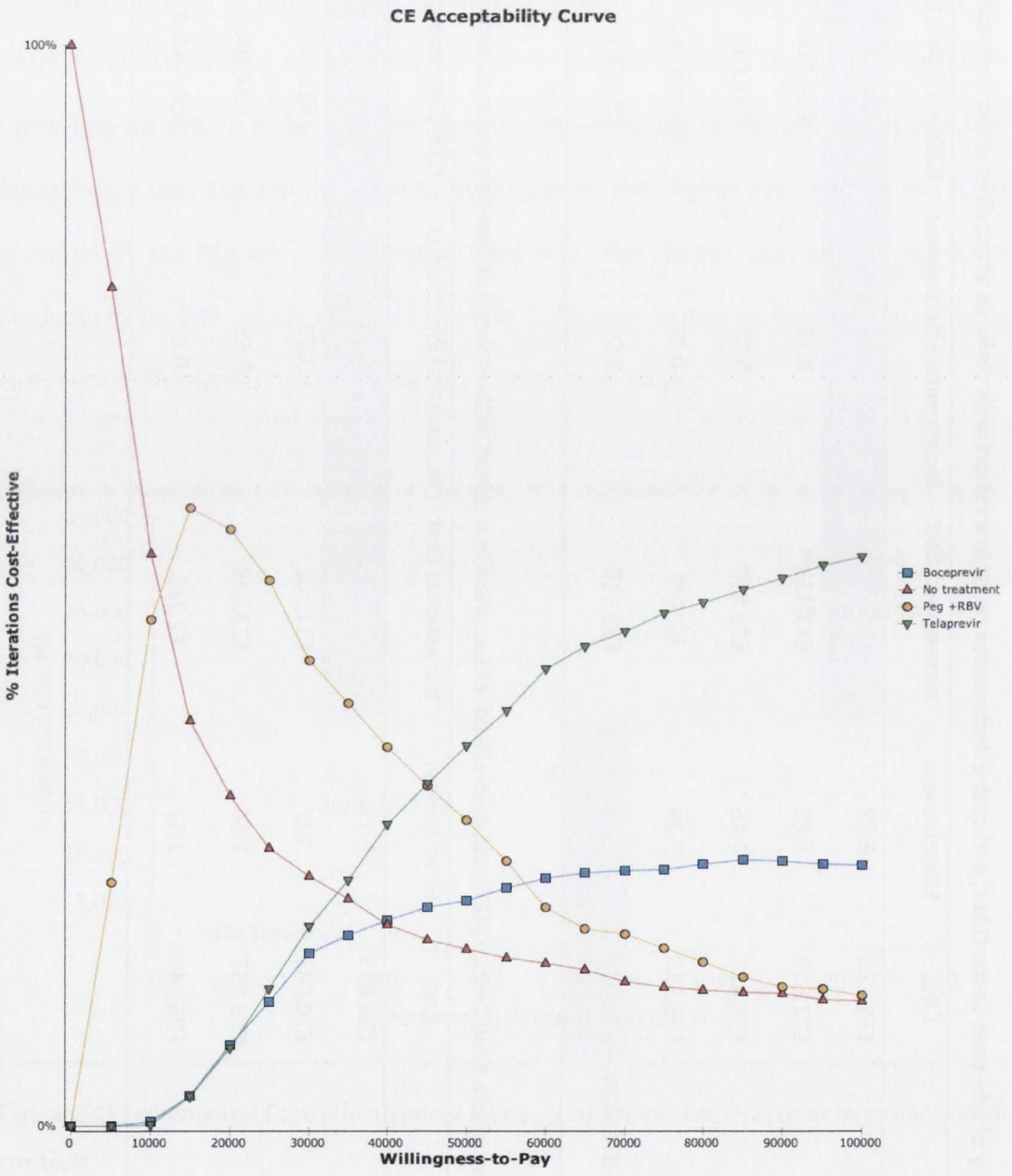



**Figure 8-20 Cost-effectiveness acceptability curve of available treatment strategies in a cirrhotic HCV cohort**

Figure 8-21 displays a scatterplot of the incremental cost-effectiveness of the treatment strategies in a cirrhotic cohort. This is further evaluated using 95% ellipses of pair-wise incremental comparisons in Figures 8-22 to 8-24.

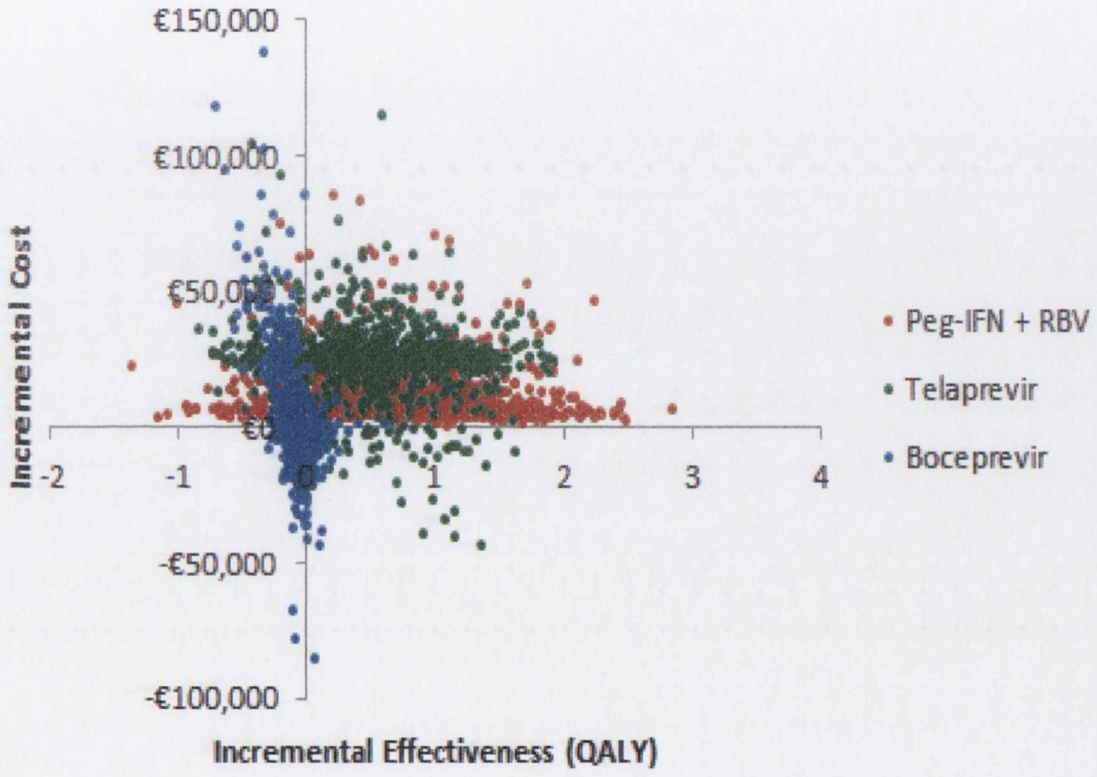



**Figure 8-21 Scatterplot of Incremental lifetime Costs versus QALYs in patients with cirrhosis** *(Peg-IFN+RBV incremental to No Treatment, Telaprevir incremental to Peg-IFN+RBV, Boceprevir incremental to Telaprevir)*

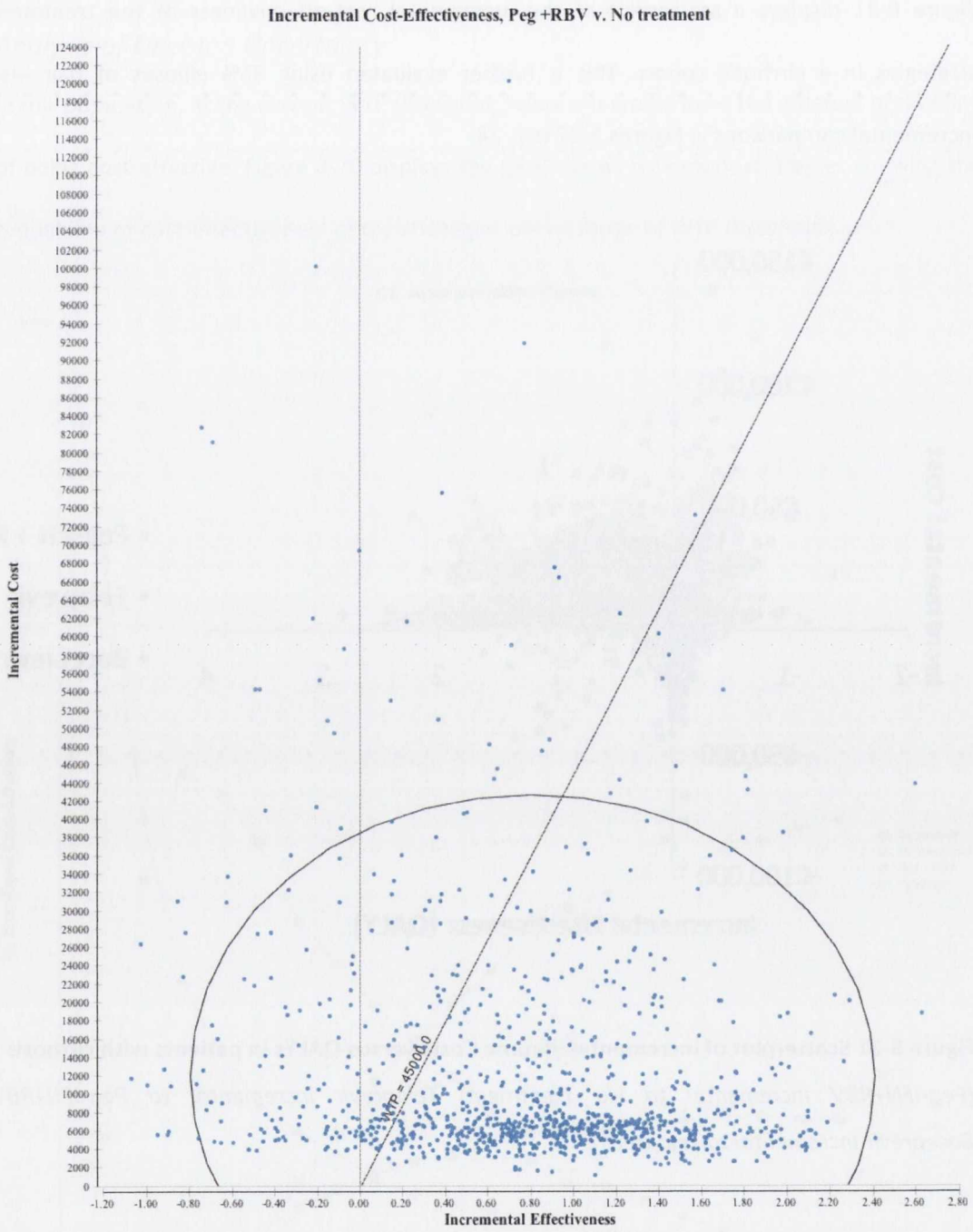



**Figure 8-22 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Peg-IFN + RBV versus No treatment in the cirrhotic HCV population**

The ellipse in Figure 8-22 demonstrates that at a willingness to pay threshold of €45,000, 79% of the iterations of the PSA would find Peg-IFN and RBV a cost-effective option when compared to No treatment in this cirrhotic population.

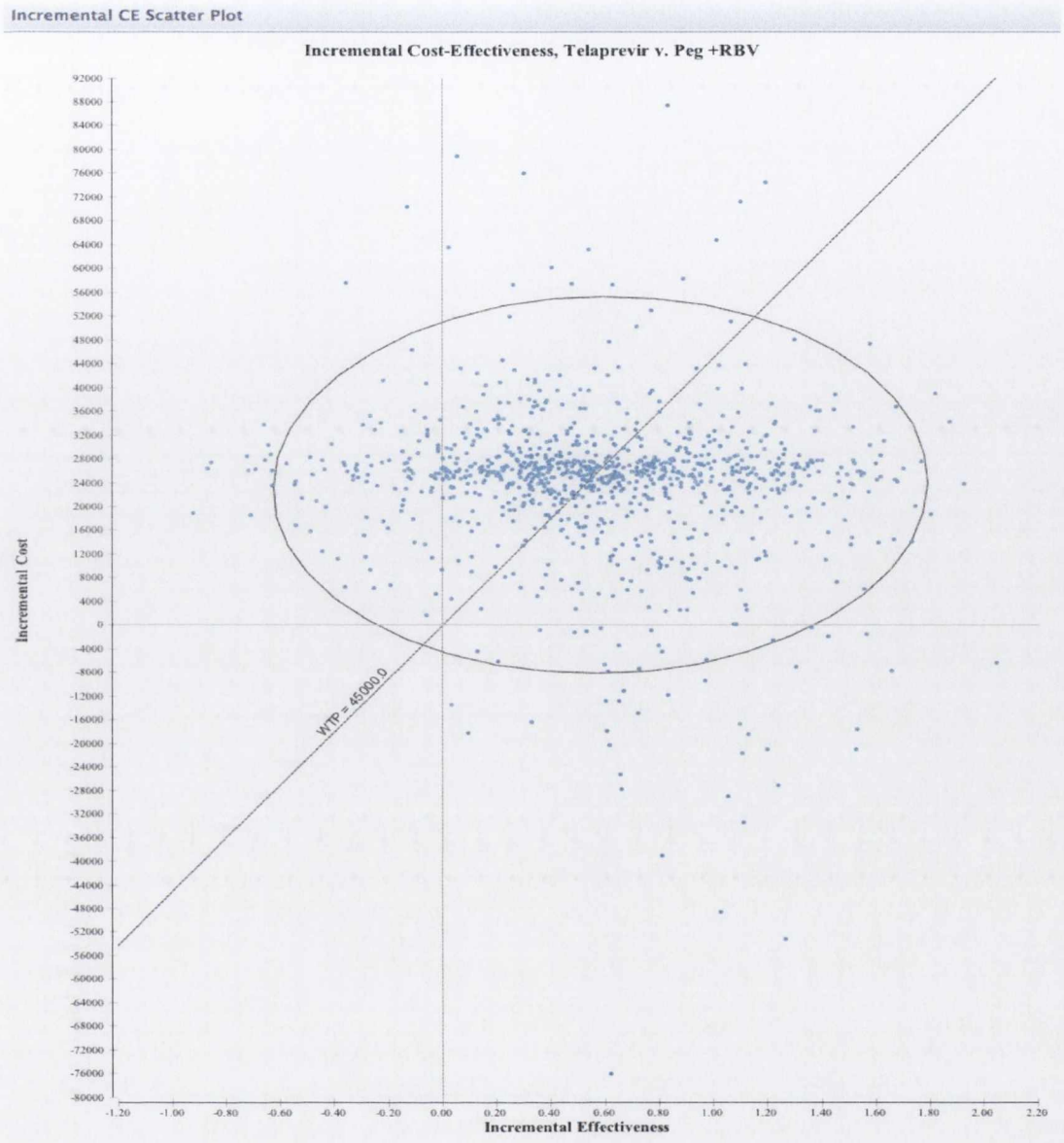



**Figure 8-23 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Telaprevir versus Peg-IFN + RBV in the cirrhotic HCV population**

The ellipse in Figure 8-23 demonstrates that at a willingness to pay threshold of €45,000, 52% of the iterations of the PSA would find Telaprevir a cost-effective option when compared to Peg-IFN and RBV. In 47% of the iterations, TEL was more costly, but more effective than Peg-IFN+RBV with an ICER under the WTP threshold (Quadrant 1) and in 5% it was less costly and more effective (Quadrant 2).

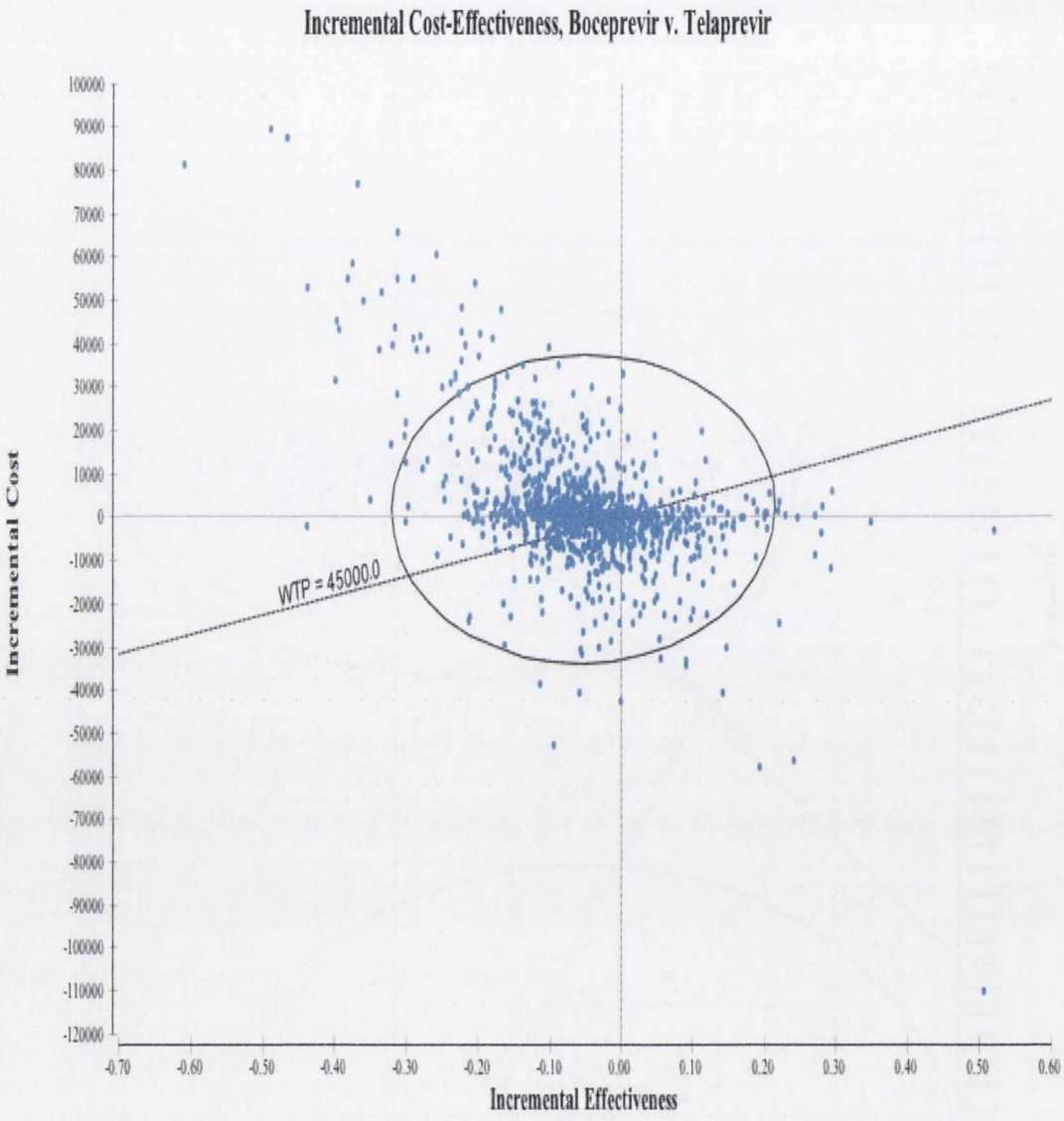



**Figure 8-24 Scatterplot ellipse demonstrating 95% CI and WTP threshold of Telaprevir versus Boceprevir in the cirrhotic HCV population**

The ellipse in Figure 8-24 demonstrates that at a willingness to pay threshold of €45,000, 21% of the iterations of the PSA would find BOC a cost-effective option when compared to Tel in this population. In 4% of the iterations, BOC was more costly but more effective than TEL with an ICER below €45,000. In 17% of the iterations BOC was less costly and more effective than TEL (Quadrant 2). The majority of the iterations (44%) were found in Quadrant 4, where BOC was more costly and less effective than TEL.

## 8.5 Discussion

Prior to the introduction of the protease inhibitors, antiviral treatment of HCV had not been assessed for its cost-effectiveness. Both boceprevir and telaprevir were found to be cost-effective treatments when compared to pegylated interferon and ribavirin (99, 100). However, pegylated interferon and ribavirin had not been assessed for its cost effectiveness when compared to no treatment. Since new treatments are generally benchmarked against the existing standard of care, it is useful to demonstrate that the standard of care itself represents value for money. This analysis has shown that treatment of HCV in Ireland with the pre-existing standard of care is a cost-effective option, with ICERs well below the willingness-to-pay threshold in all populations considered. Additionally, boceprevir and telaprevir were both cost-effective treatment options when compared individually to pegylated interferon and ribavirin in this independently produced model, validating the assessments previously carried out by the NCPE on company models. This is in accordance with published literature from other healthcare jurisdictions but it has never previously been demonstrated in Ireland (138, 211-214). It represents an important piece of evidence at this time, when the cost of treating HCV is being hotly debated both nationally and internationally (104, 215). This is a time of rapid evolution in HCV therapeutics and drug therapies which have come to market or are due for release shortly will change the treatment paradigms significantly (164). The price point of the new agents is such that many health care agencies are struggling to fund them, even in resource rich countries (104). In such an environment, it is important to establish the cost-effectiveness of currently available treatment options as the price and cost-effectiveness of new agents will be compared against them. In work carried out previously in the high-cost areas of anti-TNF agents for rheumatoid arthritis and treatments for multiple sclerosis, the available treatments were not found to be cost-effective in the Irish setting (216, 217). Thus, the debate around the budget impact and funding of HCV treatment should be tempered with the acknowledgement that this is a cost-effective treatment arena in contrast to other publicly

reimbursed disease areas. The controversy around funding HCV treatment is interesting also for the issues it raises around societal preferences on the distribution of scarce health resources. Work done previously by Ubel et al which examined public preferences with regards to liver transplantation allocation, found that people were less likely to allocate organs to patients perceived to have an element of personal responsibility with regards to the aetiology of their illness (218-220). As the majority of patients infected with HCV have IVDU as their acquisition risk factor it is possible that there is a conscious or subconscious bias against providing expensive treatments to patients who are perceived to have had a role in the development of their illness and the potential to re-infect themselves post-treatment. The published re-infection rates in Irish HCV cohorts are very low and treatment outcomes in HCV infected drug users have been shown to be as good as those with iatrogenic HCV (89). Therefore, concerns around treatment efficacy and reinfection should not be reasons to withhold treatments from this population.

The cost of untreated HCV rises significantly with disease progression as demonstrated in the scenario considering only cirrhotic patients. In that scenario, the lifetime costs associated with the natural history arm of the model were substantially greater than the costs generated by the natural history arm of the model when considered under conditions of the baseline population (20% cirrhotic) or the 100% mild/moderate HCV population. At the same time, the QALY gains were substantially lower, as patients with cirrhosis who are cured of HCV remain at risk of progression to decompensation and hepatocellular carcinoma, albeit at a much reduced rate (203). Epidemiological work carried out by the National Drug Treatment Centre would suggest that the peak of incident HCV infections in Ireland occurred in the mid-nineties(71). Therefore, the majority of HCV patients will now have been infected for 20 years or more. Given the natural history of HCV, these patients will develop cirrhosis at an increased rate in the near future (23). While treatment of HCV in cirrhotic patients is cost-effective, this work would suggest that there would be reduced costs and increased health benefits for both the

individual and the healthcare system if patients were treated for HCV before they developed cirrhosis. The benefit of early treatment of HCV is re-enforced by the sensitivity of the model to the time horizon, which would suggest that the longer people are likely to live after their HCV is treated, the greater the health gains seen.

Under the conditions of the baseline population, boceprevir was the preferred agent for HCV triple therapy from a cost-effectiveness perspective. There was considerable uncertainty around this result however. The CEAC demonstrates that at current WTP thresholds, boceprevir had the highest probability of cost-effectiveness of the available options at 50% probability of cost-effectiveness. Peg + RBV were the correct decision versus no treatment the majority of the time in all populations, supporting the cost-effectiveness of HCV with the previous standard of care. In the 100% cirrhotic population, telaprevir was the preferred choice the majority of the time when compared to Peg-IFN + RBV or boceprevir. Under deterministic sensitivity analysis, there were no scenarios in the mild/moderate HCV cohort, where telaprevir had a more favourable ICER than boceprevir. Conversely, in the cirrhotic cohort under deterministic sensitivity analysis, boceprevir was dominated by telaprevir under all tested conditions. *(Supplemental Appendix 4)* This suggests that, from a cost-effectiveness perspective, non-cirrhotic patients should be treated with boceprevir, while cirrhotic patients should be treated with telaprevir. This could be considered in clinical guidelines, once individual patient characteristics allowed for a choice between agents.

## 8.6 Limitations

The model efficacy is populated from the evidence supplied in the Phase 3 trials of boceprevir and telaprevir (94-97, 188). There were a number of limitations to the evidence supplied by these trials. Potentially important baseline genetic markers for interferon-responsiveness, such as IL-28B were not collected as part of the trials as the importance of this characteristic was not appreciated at the time of trial design. Therefore, the patients in the trials were not

stratified to account for this variable and it could not be controlled for in our network meta-analysis. It is possible that there were more patients with more favourable IL28B haplotypes treated with one of the drugs in question versus another, but there is no way of knowing this and therefore this variable was not incorporated into this model. The advent of interferon-free regimens will make this issue less important in the comparison of future agents (26). Similarly, the SVR rates of patients depending on their rapid virological responses were not reported out in the trials and therefore could not be considered separately from an efficacy perspective in this analysis. The lower cost of treatment and the reduced disutility of shorter course treatment are adjusted in the arms considering patients who achieved an RVR.

The model assumes that the real-world effectiveness of the treatments will mirror the efficacy results of the trials. This may not be a true assumption and we await with interest the publication of the cost and effectiveness data from the ICORN HCV PI registry which was established with the re-imbursement of the HCV protease inhibitors in Ireland. It is hoped to re-run the analysis, populated with real-world registry data and compare the results with the data presented here.

The model does not allow for HCV re-infection. The rates of re-infection reported in treated patients in Ireland have been very low to date (89). Reducing the efficacy rates of the treatment regimens substantially in the one-way sensitivity analysis, did not significantly affect the ICERs which suggests that extremely high re-infection rates would be required to change the finding on the cost-effectiveness of HCV treatment.

The costs and utility estimates used in the model are derived from patients attending two hepatology centres in Ireland and therefore may not be generalisable outside of these centres. However, the centres provide care to greater than 4000 patients which is approximately half the HCV patients currently engaged in care in Ireland (2). It is reasonable to assume that they are representative of the larger HCV population in Ireland.

The transition probabilities used in the trial were largely drawn from a UK study (160). They are widely used and accepted in the literature but it is possible that they may not be representative of disease progression in an Irish HCV cohort. Where possible, they have been supplemented by Irish data for disease progression (40, 204, 210). In the absence of specific Irish transition probabilities they are reasonable surrogates and they were not found to have an effect on the model in one-way sensitivity analysis.

## 8.7 Conclusions

Treatment of HCV in Ireland is cost-effective in patients with mild HCV and in those with cirrhosis associated with HCV. Either protease inhibitor is cost-effective when compared with the previous standard of care. When compared with each other, the choice of agent depends on the population being considered. Boceprevir is the most cost-effective protease inhibitor in a non-cirrhotic cohort. Telaprevir is more cost-effective in a cirrhotic cohort. The evidence would suggest that the health care costs are lower and the HRQOL gains higher when patients are treated for HCV prior to developing cirrhosis.

# Chapter 9

# 9 Conclusion

## 9.1 The Budget Impact of HCV treatment with Peg-IFN and RBV

Since the discovery of the HCV virus in 1989, enormous strides have been made in treating this chronic insidious disease which is estimated to infect 20,000 – 50,000 people in Ireland. The combination of Peg-IFN and RBV offered the first chance of cure to a substantial number of patients, especially those infected with HCV Genotype 3. At the time of its introduction, Peg-IFN and RBV sparked international interest from a cost-effectiveness perspective and was found to be a cost-effective intervention in the US and UK, but this was never assessed in an Irish setting. Without an Irish treatment registry, the number of treated patients, their demographics, and the drug cost of Peg-IFN and RBV was not readily available. The analysis of the PCRS database performed as part of this thesis, gave the first estimates of the numbers treated and the budget impact of that drug therapy. It also gave decision makers who were examining the rollout of HCV DAAs, an indication of the capacity of the HCV treatment clinics at a time when this was very germane to budget impact estimates. In contrast to reports from the UK, co-prescribing of haematological growth factors in the setting of Peg-IFN and RBV was found to be common and likely to be responsible for a substantial additional cost in the setting of treatment with PI-based triple therapy. Demonstrating this prescribing pattern in Ireland allowed the inclusion of this drug cost into the eventual cost-effectiveness model and strengthened its validity.

## 9.2 The Cost of Untreated HCV

Given the rapidly expanding HCV armamentarium identified during horizon scanning in 2011, valid estimates of the cost of HCV care in Ireland were urgently needed in order to assess and

inform the accuracy of company submissions. There was no data on the cost of care in this disease area in Ireland prior to the work done for this thesis.

The direct medical cost associated with Hepatitis C care was found to be substantial and increased exponentially with progression of liver disease. In contrast, the follow-up cost of patients with a sustained virological response was low in comparison to patients with chronic infection. This cost data was required to populate the cost-effectiveness model and has also been useful to clinicians and decision makers establishing business plans for expansion of and improvement to, clinical services for HCV.

## 9.3 The HRQoL of Untreated HCV

The valuation of cost and consequences is essential for cost-effectiveness analysis. Health state utility data has been shown to vary depending on the population studied and therefore it is preferable to have local utility values if possible. The publications documenting health-state utility in HCV are few and there are none describing utilities elicited using the novel EQ-5D 5-level questionnaire or done in Irish populations. This thesis established health-state utilities across the full spectrum of HCV disease in an Irish population. HCV was found to have a significant impact on HRQoL even at mild stages of liver fibrosis. There was a marked decrease in HRQoL as patients developed more severe cirrhosis. Treating HCV resulted in an improvement in HRQoL to levels seen in the general population. The mean time post treatment in the cohort was 5 years which suggests that the improvement is sustained and both non-cirrhotic and cirrhotic patients reported similar values. This is valuable information both nationally and internationally as health systems grapple with the problem of funding HCV DAAs.

## 9.4 The Relative Efficacy of 1st Generation HCV Protease Inhibitors

Comparative efficacy estimates are essential in performing cost-effectiveness analysis. Naïve comparisons of efficacy across trials are not encouraged as they do not account for between-trial variability. There were no head-to-head trials performed examining the comparative efficacy of the 1st generation PIs and the work presented in this thesis provided the first published estimates of the comparative efficacy of boceprevir and telaprevir. Overall no differences in efficacy were detected, other than in the population that had had a previous treatment relapse. In that population, telaprevir had greater efficacy than boceprevir. This was important information for clinicians and decision makers but has now been superseded with the arrival of the newer DAA's. They will be challenging to compare using network meta-analysis methodology as many of the Phase 3 trials were designed without a comparator arm. One approach would be to develop a historical benchmark of efficacy and compare the efficacy of new therapies with that.

## 9.5 The Cost-effectiveness of HCV Treatment in Ireland

There had been no analysis of the cost-effectiveness of HCV treatment in the Irish setting prior to the work presented in this thesis. Given that new therapies are compared to the pre-existing standard of care, it is important to establish that the existing therapies represent value for money. In areas where this has been examined to date in Ireland (Rheumatoid Arthritis and Multiple Sclerosis), the original therapies were not found to be cost-effective. In contrast, treatment of HCV in Ireland is cost-effective in patients with mild HCV and in those with cirrhosis associated with HCV. Either protease inhibitor is cost-effective when compared with the previous standard of care, Peg-IFN + RBV. Peg-IFN +RBV was found to be cost-effective when compared to not treating HCV. When compared with each other, the choice of agent

depends on the population being considered. Boceprevir is the most cost-effective protease inhibitor in a non-cirrhotic cohort. Telaprevir is more cost-effective in a cirrhotic cohort. The evidence would suggest that the health care costs are lower and the HRQOL gains higher when patients are treated for HCV prior to developing cirrhosis.

Current policy dictates that those with the highest clinical need are the only ones presently receiving HCV treatment with DAAs. This is driven by a need to limit the budget impact of HCV treatment. Analysis of the DAAs was beyond the scope of this research thesis, so no conclusions can be drawn about the cost-effectiveness of the DAAs in Ireland. Similarly to boceprevir and telaprevir, they have been found to be cost-effective from company submissions and in that case it is likely that it will hold true that treating patients prior to the development of cirrhosis will ultimately deliver more health benefit than waiting until their disease has progressed. The model created as part of this work can be adapted to include the new agents and test this hypothesis.

## 9.6 Conclusion

This thesis comprehensively addresses the question of the cost-effectiveness of HCV treatment with 1$^{st}$ generation Protease Inhibitors in Ireland. It provides valuable information on the costs and consequences of HCV infection and treatment which continue to be relevant to national and international stakeholders. The development of an academic, independent model of HCV treatment populated with Irish data, establishes a platform for the future analysis of HCV care. HCV therapeutics presents a huge opportunity for population health gain but remains a challenge to fund, ensuring that the cost-effectiveness of strategies in this disease area will continue to be subject to scrutiny and interest.

# *Publications*

# Publications

## Peer- Reviewed Journal Articles

1. "Hepatitis C in the Era of Direct-Acting Antivirals: Real-World Costs of Untreated Chronic Hepatitis C; a Cross-sectional Study" **J Kieran** et al. *BMC Infectious Diseases, Vol 15:417 26/10/ 2015* PMID: 26503519
2. "The Budget Impact of Hepatitis C Treatment in Ireland 2001-2012" **J Kieran,** K Bennett, C Bergin, S Norris, M Barry. *IMJ 2015 Jun;108(6):166-9* PMID: 26182797
3. "The Relative Efficacy of Boceprevir and Telaprevir in the treatment of Hepatitis C virus Genotype 1" **J Kieran**, S Schmitz, A O'Leary, C Walsh, C Bergin, S Norris, M Barry. *Clin Infect Dis. 2013 Jan;56(2):228-35.* PMID: 23074300
4. "Reply to Calgano et al." **J Kieran**, S Schmitz, A O'Leary, C Walsh, C Bergin, S Norris, M Barry. *Clin Infect Dis. 2013 Jun;56(11):1678-9* PMID: 23418277

## Oral Presentations/Poster

1. "New Drugs for Hepatitis C; Effective but can we Afford Them" Invited Speaker, Irish Association of Pharmacologists, Dublin, November 2014
2. "Hepatitis C in the Era of Direct-Acting Antivirals: Real-World Costs of Untreated Chronic Hepatitis C" J Kieran, S Norris, R Merriman, P.A. McCormick, S McKiernan, D Houlihan, C Walsh, C Bergin, M Barry. Poster 30, ISGE Winter Meeting 2014
3. "Health-State Utilities in Patients with Different Stages of Hepatitis C Infection" J Kieran, R Adams, J-L Chin, H Mushtaq, P.A. McCormick, S McKiernan, C Walsh, R Merriman, C Bergin, S Norris, M Barry. Poster 29, ISGE Winter Meeting 2014
4. "The Budget Impact in Ireland of the Treatment of Hepatitis C with Direct Acting Antivirals" **Kieran J**, Bennett K, O'Leary A, Bergin C, Norris S, Barry M. Infectious Diseases Society of Ireland 2013

5. "PHS59 Demographic and Health-state Utilities in Irish patients with Hepatitis C; Use of the 5-Level EQ-5D Questionnaire" J Kieran, H Mustaq, C Bergin, S Norris, M Barry. ISPOR Berlin 2012. *Value in Health 2012 Nov;15(7):A528*
6. "A Bayesian Mixed Treatment Comparison Evaluating the Relative Efficacy of Currently Licensed HCV Protease Inhibitors for the Treatment of HCV Genotype 1 Infection" **Kieran J,** Schmitz S, O'Leary A, Walsh C, Bergin C, Norris S, Barry M.. EASL Barcelona 2012. *J Hepatology Apr2012(S2):S443*
7. "The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of HCV Genotype 1" **Kieran J,** Schmitz S, O'Leary A, Walsh C, Bergin C, Norris S, Barry M.. Infectious Diseases Society of Ireland 2012 (Oral Presentation)
8. "A Bayesian Mixed Treatment Comparison Evaluating the Relative Efficacy of Currently Licensed HCV Protease Inhibitors for the Treatment of HCV Genotype 1 Infection" **Kieran J,** Schmitz S, O'Leary A, Walsh C, Bergin C, Norris S, Barry M.. Irish Society of Gastroenterology April 2012 (Oral Presentation)

## Under Review

1. Health-State Utilities in Patients with Different Stages of Hepatitis C Infection; Use of the novel 5-Level EQ-5D. J Kieran et al. *Under Review, Journal of Viral Hepatitis, January 2016*

# *Appendices*

# Supplementary Appendices

## Appendix 1 – Pre-Liver Transplantation work-up

| Outpatient Reviews | UNITS |
|---|---|
| Transplant co-ordinators | 120 |
| Anaesthetic review | 32 |
| Transplant surgical review 2-4 | 51 |
| Dietician review | 60 |
| Dental Review | 60 |
| Psychiatrist Review | 60 |
| Hepatology review | 20 |
| Laboratory | |
| FBC | 1 |
| COAG | 1 |
| Group and Hold | 1 |
| Liver profile | 1 |
| Renal profile | 1 |
| Auto-antibodies | 1 |
| Immunoglobulins | 1 |
| AFP | 1 |
| alpha-1-antitrypsin +bone profile | 1 |
| Caeruloplasmin | 1 |
| Copper | 1 |
| HLA typing | 1 |
| Hepatitis A antibody | 1 |
| Hepatitis B Surface Antigen | 1 |
| Hepatitis C Antibody | 1 |
| Hepatitis C genotype | 1 |
| Hepatitis C viral load | 1 |
| CMV IgG | 1 |
| EBV IgG | 1 |
| HSV IgG | 1 |

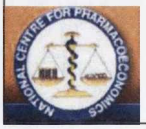
| | |
|---|---|
| VZV IgG | 1 |
| Toxoplasma IgG | 1 |
| Adenovirus IgG | 1 |
| HIV Antibody | 1 |
| 24hour urine collection for protein and GFR | 2 |
| **Radiology** | |
| CXR | 1 |
| OPG | 1 |
| CT abdomen | 1 |
| MRI liver (not standard) | 1 |
| Pelvic U/S (not standard) | 1 |
| **Cardiac** | |
| ECG | 1 |
| ECHO | 1 |
| Right heart studies (<5%) | 0.1 |
| **Respiratory** | |
| Pulmonary Function Tests | 1 |
| ABG | 1 |

# Appendix 2 Health-Related Quality of Life Questionnaire

## Quality of Life Questionnaire

Department of Hepatology

St James Hospital
Dublin




Data sheet No _____

**Some Background Information** Date: _____

- **Age**: _____years **Initials**: _____
- **Gender**: Male ☐ Female ☐
- **Country of Birth**: Ireland ☐ Other EU ☐ Non-EU Europe ☐

South-East Asia ☐ China ☐ Africa ☐ Other _____

- **Marital status**

Single ☐ Married ☐ Separated ☐ Divorced ☐ Civil Partnership ☐ Widowed ☐

- **Education**

Years spent in full-time education _____years

- **Year of Diagnosis** _____
- **Employment**

Full-time Employment ☐ Part-time Employment ☐ Unemployed ☐ House-duties ☐

Asylum-seeker ☐ Student ☐ Retired ☐

*Continued on next page*

***For Office Use Only*** MOT: COO IDU Trans Inter Unk

ALT _____ Bilirubin _____ Creatinine_____ INR _____ plt _____

AFP _____ AST _____ Alb _____

Genotype_____ PCR + Y N viral load_____ Date: _____

Cirrhosis on U/S Y N Biopsy: Y N Stage _____ Year_____

Ever:

Ascites Y N Varices Y N Variceal bleed Y N Encephalopathy Y N HRS Y N

Treatment Y N Year_____ SVR Y N if no: relapse Partial Non

Liver –related hospital admission in the past year Y N if yes : how many _____

4

**Some questions about the way you are TODAY**
Under each heading, please tick the ONE box that best describes your health **TODAY**

**MOBILITY**
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

**SELF-CARE**
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

**PAIN/DISCOMFORT**
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

**ANXIETY/DEPRESSION**
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

5

*Continued on next page*

We would like to know how good or bad your health is **TODAY**

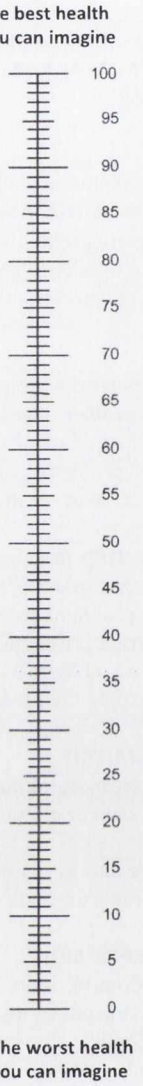
This scale is numbered from **0** to **100**
**100** means the best health you can imagine.
**0** means the worst health you can imagine.

Mark an **X** the scale to indicate how your health is **TODAY**

Now, please write the number you marked in the scale in the box below

**YOUR HEALTH TODAY =** ☐

*Thank you for taking the time to answer this questionnaire. Please hand it back to the doctor that sees you*




6

# Appendix 3 – Search Strategy and WinBUGs Code

Search Strategy

**Search strategy and inclusion criteria for literature review.**

**Literature Search strategies**

All strategies were tried and the search revealing the greatest number of results was chosen.

Duplicates were removed.

**PubMed**

**Keyword search**

**Limits Activated:** Humans, Randomized Controlled Trial, All Adult: 18+ years

1. Telaprevir
2. Boceprevir
3. #1 OR #2

Alternative Search Strategy - MESH

4. Telaprevir[mesh]
5. Boceprevir[mesh]
6. #4 OR #5
7. #3 OR #6

**Results: 19**

**EMBASE.COM**

**Keyword**

**Limits** = Randomized controlled trial, Human, Adult: 18 to 64 years, Aged: 65+ years

1. Telaprevir
2. Boceprevir

**Subject Heading / Emtree Search**

**Limits** = Randomized controlled trial, Human, Only in English, Adult: 18 to 64 years, Aged: 65+ years

1. 'Telaprevir'/exp
2. 'Boceprevir'/exp

**Results: 26**

The keyword search was repeated for the Cochrane Review Database and the Science Citation Index.

**Results: 0**

**Hand search of Conference Abstracts**

**Subject Heading: Hepatitis C – Treatments; Hepatitis C: Drug Development; Hepatitis C Clinical Advances and Therapy; Viral Hepatitis g. Hepatitis C – Clinical (Therapy)**
**Textwords: Boceprevir OR Telaprevir**

| Conference | Titles | Abstracts | Included |
|---|---|---|---|
| **EASL 2010** | 31-39;53-60;236-310<br>90 total<br>86 excluded on title | 56- not criteria,<br>256- not criteria<br>274- duplicate<br>290- duplicate | 0 |
| **AASLD 2010** | 797-836;895-1059;79-84;223-228<br>113 total<br>112 excluded on title | 227- doesn't fit criteria | 0 |
| **EASL 2011** | 85<br>77 excluded on title | 8- duplicate | 0 |
| **AASLD 2011- DDW** | 10<br>6 excluded on title | 4<br>3 didn't meet criteria | 1 |
| **AASLD 2011 – liver week** | 21<br>19 excluded on title | 1 – follow up study<br>1 – not criteria | 0 |
| **Total** | 234 | 5 - not criteria<br>14 – duplicates<br>19 total | 1 included |

WinBUGs code

```
model{
for (i in 1:N.c){
svr.c[i] ~ dbin(p.c[i],n.c[i])   ## Likelihood
logit(p.c[i]) <- mu[i]  }        ## Model

for (i in 1:N.t){
svr.t[i] ~ dbin(p.t[i],n.t[i])   ## Likelihood
logit(p.t[i]) <- mu[study[i]] + theta[i]        ## Model
theta[i] <- lor.total[study[i]] + gamma*(Cirr[study[i]]-Cirr.bar) }   ## Meta regression

for (i in 1:N.c){lor.total[i] <- mu.total[drug[i]] }     ## Fixed Effects

IC<- mu.total[1] - mu.total[2]        ## Indirect Comparison

## Priors ##
for (i in 1:N.c){mu[i] ~ dnorm(0,1.0E-6)}
for (i in 1:2){mu.total[i] ~ dnorm(0,1.0E-6)}
gamma ~ dnorm(0,1.0E-6)

Cirr.bar <- mean(Cirr[])     ## extra variable
}
```

Input Data

*Naive Patients:*

```
list(
N.c = 6,
N.t = 9,
study = c(1,2,2,3,4,5,5,6,6),
n.c =c(361,75,82,63,104,363),
svr.c = c(158,31,38,31,39,137),
n.t = c(363,79,79,81,126,103,103,368,366),
svr.t = c(271,48,53,56,92,58,77,233,242)
drug = c(1,1,1,1,2,2),
Cirr = c(0.06,0,0,0,0.07,0.09)
)
```

*Experienced Patients:*

```
list(
```

```
N.c = 4,
N.t = 6,
study = c(1,1,2,3,3,4),
n.c =c(132,114,80,67),
svr.c = c(22,16,17,14),
n.t = c(266,264,115,162,161,134),
svr.t = c(171,175,59,95,107,86),
drug = c(1,1,2,2),
Cirr = c(0.26,0.14,0.12,0.23)
)
```

**This is the meta-regression model for cirrhosis; other confounders are adjusted for in the same way*

## Appendix 4 – One-way Sensitivity Analysis and Pair-wise Tornado diagrams

| NAME | DESCRIPTION | VALUE | LOW | HIGH | ICER | Basecase | LOW | High |
|---|---|---|---|---|---|---|---|---|
| cAnaemia | Cost of managing Anaemia 2000-2009 | 4728.0 | 4149 | 5307 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20,408 | 20657 |
| | | | | | BOC | 24234 | 24170 | 24298 |
| | | | | | TEL | 128082 | 128466 | 127699 |
| cBaseline | Cost of baseline HCV workup | 1523.93 | 1218 | 1827 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 24234 | 24234 |
| | | | | | TEL | 128082 | 128082 | 128082 |
| cBOC24 | cost of 24 weeks of Boceprevir | 19333.44 | 15466.75 | 23200.13 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 21301 | 27166 |
| | | | | | TEL | 128082 | 153189 | 102975 |
| cBOC32 | cost of 32 weeks of Boceprevir treatment | 25777.92 | 20622.34 | 30933.5 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 21613 | 26854 |
| | | | | | TEL | 128082 | 150020 | 105644 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| cBOC44 | cost of 44 weeks of Boceprevir | 35444.64 | 28355.71 | 42533.57 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 21752 | 26715 |
| | | | | | TEL | 128082 | 149331 | 106834 |
| cCompcirrhosis | Cost of Compensated cirrhosis | 1790.0 | 990 | 3164 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 21043 | 19656 |
| | | | | | BOC | 24234 | 24509 | 23761 |
| | | | | | TEL | 128082 | 128392 | 127550 |
| cDecomp | cost of Decompensated cirrhosis | 6541.0 | 4513 | 8981 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 21232 | 19692 |
| | | | | | BOC | 24234 | 24548 | 23856 |
| | | | | | TEL | 128082 | 128205 | 127935 |
| cHCC | cost of HCC | 27652.0 | 22497 | 32408 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20911 | 20184 |
| | | | | | BOC | 24234 | 24570 | 23924 |
| | | | | | TEL | 128082 | 128213 | 127962 |
| cMild | Cost in Mild Healthstate | 398.0 | 336 | 482 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20950 | 19967 |
| | | | | | BOC | 24234 | 24489 | 23887 |
| | | | | | TEL | 128082 | 128467 | 127560 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| cModerate | cost of moderate healthstate | 417.0 | 335 | 503 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20740 | 20315 |
| | | | | | BOC | 24234 | 24397 | 24062 |
| | | | | | TEL | 128082 | 128146 | 128015 |
| cMonitoring24 | Cost of monitoring 24 weeks of Treatment | 2738.0 | 2464.2 | 3011.8 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 24234 | 24234 |
| | | | | | TEL | 128082 | 125471 | 130693 |
| cMonitoring28 | cost of monitoring 28 weeks of treatment | 2916.0 | 2624.4 | 3207.6 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 24013 | 24455 |
| | | | | | TEL | 128082 | 129976 | 126189 |
| cMonitoring48 | cost of monitoring for 48 weeks of treatment | 3856.0 | 3470.4 | 4241.6 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 19992 | 21074 |
| | | | | | BOC | 24234 | 24631 | 23827 |
| | | | | | TEL | 128082 | 128329 | 127836 |
| cOPD | cost of OPD visit | 136.0 | 133 | 139 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20531 | 20534 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | BOC | 24234 | 24232 | 24235 |
| | | | | | TEL | 128082 | 128088 | 128076 |
| cPEG_RBV24 | cost of PEg+RBV for 24 weeks | 7773.73 | 6218.98 | 9328.48 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20533 | 20533 |
| | | | | | BOC | 24234 | 24234 | 24234 |
| | | | | | TEL | 128082 | 113256 | 142908 |
| cPeg_RBV28 | cost of Peg +RBV for 28 weeks | 9096.35 | 7255.48 | 10883.22 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 22838 | 25588 |
| | | | | | TEL | 128082 | 140035 | 116480 |
| cPeg_RBV48 | cost of 48 weeks Peg + RBV | 15547.46 | 12437.97 | 18656.95 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 16170 | 24895 |
| | | | | | BOC | 24234 | 27436 | 21031 |
| | | | | | TEL | 128082 | 130070 | 126094 |
| cPost_treatment | cost of post-treatment monitoring | 708.33 | 566 | 850 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 203008 | 20756 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 128082 | 128082 |
| cPosttransplant | Cost of Post-transplant state | 5337.0 | 4942 | 5799 | NT | 0 | 0 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | PR | 20533 | 20530 | 20536 |
| | | | | | BOC | 24234 | 24231 | 24236 |
| | | | | | TEL | 128082 | 128081 | 128083 |
| cSVR | cost of followup for SVR patient | 82.0 | 66 | 101 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20393 | 20699 |
| | | | | | BOC | 24234 | 24105 | 24386 |
| | | | | | TEL | 128082 | 128028 | 128147 |
| cTEL | Drug cost of telaprevir | 26334.0 | 21067.2 | 31600.8 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 34064 | 222100 |
| cTransplant | Cost of Transplant 1st year | 137176.0 | 136024 | 138306 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20537 | 20528 |
| | | | | | BOC | 24234 | 24237 | 24230 |
| | | | | | TEL | 128082 | 128083 | 128081 |
| Discontinue_weeks _BOC_NORGT | mean no of weeks of therapy with BOC if no RGT | 20.0 | 16 | 24 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 22130 | 26406 |
| | | | | | TEL | 128082 | 153493 | 105048 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Discontinue_weeks _BOCRGT | mean no of weeks of treatment with BOC before discontinuation | 15.0 | 12 | 18 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 22850 | 25662 |
| | | | | | TEL | 128082 | 143646 | 113156 |
| discount_rate | discount rate | 0.05 | 0 | 0.1 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 2506 | 53998 |
| | | | | | BOC | 24234 | 4487 | 53925 |
| | | | | | TEL | 128082 | 71349 | 160083 |
| pAnaemia_BOC | probability of BOC side-effects | 0.5 | 0.34 | 0.66 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 23323 | 25146 |
| | | | | | TEL | 128082 | 147416 | 112037 |
| pAnaemia_TEL | prob of anaemia for Telaprevir | 0.37 | 0.13 | 0.71 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 100954 | 188678 |
| pBOCRVR | probability of RVR with Boceprevir | 0.56 | 0.5 | 0.62 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |

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|---|---|---|---|---|---|---|---|---|
| | | | | | BOC | 24234 | 24980 | 23497 |
| | | | | | TEL | 128082 | 116489 | 141073 |
| pCirrhosis | probability of cirrhosis in treatment arms | 0.2 | 0 | 0.4 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 23662 | 17978 |
| | | | | | BOC | 24234 | 17045 | 30677 |
| | | | | | TEL | 128082 | 186230 | 77787 |
| pComptoDecomp | Transition probability of Compensated to Decompensated cirrhosis | 0.039 | 0.016 | 0.042 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 23070 | 20299 |
| | | | | | BOC | 24234 | 26818 | 23992 |
| | | | | | TEL | 128082 | 132732 | 127616 |
| pComptoHCC | probability of transition from Compensated cirrhosis to HCC | 0.014 | 0.013 | 0.04 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20633 | 17985 |
| | | | | | BOC | 24234 | 24359 | 21779 |
| | | | | | TEL | 128082 | 128232 | 125104 |
| pDecompensateSVR | prob of decompensation post-SVR | 0.12 | 0.06 | 0.24 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20554 | 20032 |
| | | | | | BOC | 24234 | 24253 | 23786 |

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|---|---|---|---|---|---|---|---|---|
| | | | | | TEL | 128082 | 128091 | 127878 |
| pDecompTodeath | pDecompToDeath | 0.13 | 0.07 | 0.27 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20765 | 20127 |
| | | | | | BOC | 24234 | 24456 | 23844 |
| | | | | | TEL | 128082 | 128351 | 127612 |
| pDecompToHCC | probability of transition from Decompensated cirrhosis to HCC | 0.014 | 0.013 | 0.04 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20435 | 20632 |
| | | | | | BOC | 24234 | 24234 | 24244 |
| | | | | | TEL | 128082 | 129012 | 126988 |
| pDecompToTranspl ant | probability of transition from Decompensated cirrhosis to Transplant | 0.02 | 0.01 | 0.04 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20214 | 21151 |
| | | | | | BOC | 24234 | 23904 | 24869 |
| | | | | | TEL | 128082 | 127452 | 129275 |
| pDiscontinue_BOC | discontinue rate of BOC no RGT | 0.3 | 0.24 | 0.36 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 23368 | 22937 |
| | | | | | TEL | 128082 | 114922 | 141482 |

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|---|---|---|---|---|---|---|---|---|
| pDiscontinueBOCRGT | Discontinuation rate of BOC given RGT | 0.23 | 0.18 | 0.28 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 21233 | 19835 |
| | | | | | BOC | 24234 | 23285 | 25187 |
| | | | | | TEL | 128082 | 128082 | 128082 |
| pDiscontinuePR | Probability of discontinuing PR | 0.44 | 0.35 | 0.53 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 126647 | 128082 |
| pDiscontinuePR_TELnoRGT | probability of dicontinuing PR on non-RGT | 0.26 | 0.18 | 0.26 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 141020 | 116163 |
| pDiscontinueTel | probability of discontinuing Telaprevir | 0.16 | 0.13 | 0.19 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 27335 | 21273 |
| | | | | | TEL | 128082 | 95848 | 165366 |
| pEPO | probability of being prescribed EPO if anaemic | 0.44 | 0.37 | 0.51 | NT | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|---|---|
| | | | | | PR | 20533 | 20412 | 20653 |
| | | | | | BOC | 24234 | 24069 | 24397 |
| | | | | | TEL | 128082 | 128624 | 127540 |
| pHCC2to5toDeath | prob of dying from HCC yr 2-4 post diagnosis | 0.26 | 0.05 | 0.15 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20118 | 20405 |
| | | | | | BOC | 24234 | 23908 | 24133 |
| | | | | | TEL | 128082 | 128408 | 128182 |
| pHCCpostSVR | prob of HCC post-SVR | 0.27 | 0.21 | 0.36 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20356 | 20795 |
| | | | | | BOC | 24234 | 24059 | 24492 |
| | | | | | TEL | 128082 | 127824 | 128462 |
| pHCCtoDeath | probability of HCC to death in year 1 | 0.53 | 0.48 | 0.57 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20425 | 20617 |
| | | | | | BOC | 24234 | 24149 | 24300 |
| | | | | | TEL | 128082 | 128167 | 128014 |
| pHCCToTransplant | probabililty of HCC to Transplant | 0.02 | 0 | 0.05 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20522 | 20547 |
| | | | | | BOC | 24234 | 24226 | 24244 |
| | | | | | TEL | 128082 | 128097 | 128060 |

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|---|---|---|---|---|---|---|---|---|
| pHCCYR2to5 | prob of moving to HCC YR 2-4 to HCC Yr 5 | 0.25 | 0.2 | 0.3 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20578 | 20494 |
| | | | | | BOC | 24234 | 24269 | 24203 |
| | | | | | TEL | 128082 | 128046 | 128113 |
| pHCVPostTranspla ntToDeath | prob of dying after 1st year post transplant while infected with HCV | 0.07 | 0.04 | 0.08 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20549 | 20528 |
| | | | | | BOC | 24234 | 24252 | 24228 |
| | | | | | TEL | 128082 | 128140 | 128066 |
| pHCVTransplantTo Death | prob of Death post-tranplant in year 1 with HCV | 0.17 | 0.1 | 0.28 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20605 | 20473 |
| | | | | | BOC | 24234 | 24319 | 24163 |
| | | | | | TEL | 128082 | 128342 | 127867 |
| pInitDecompCirr | Probability of Initially having Decompensated Cirrhosis | 0.39 | 0.31 | 0.47 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20079 | 21010 |
| | | | | | BOC | 24234 | 23474 | 25038 |
| | | | | | TEL | 128082 | 126635 | 129561 |

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|---|---|---|---|---|---|---|---|---|
| pInitModerate | probability of initially having Moderate HCV | 0.16 | 0.08 | 0.32 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 22440 | 17332 |
| | | | | | BOC | 24234 | 26100 | 21034 |
| | | | | | TEL | 128082 | 131178 | 122283 |
| pMildtoMode | transition probability of Mild to Moderate | 0.025 | 0.0125 | 0.04 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 23044 | 18438 |
| | | | | | BOC | 24234 | 26711 | 22131 |
| | | | | | TEL | 128082 | 131795 | 124655 |
| pModtoComp | probability of transition from Moderate to Compensated cirrhosis | 0.037 | 0.0185 | 0.073 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 24837 | 16277 |
| | | | | | BOC | 24234 | 28446 | 19933 |
| | | | | | TEL | 128082 | 134152 | 120829 |
| pPEGRBVcirrhosis SVR | probability of cirrhotic attaining SVR on Peg + RBV | 0.26 | 0.12 | 0.4 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 24586 | 17520 |
| | | | | | BOC | 24234 | 28875 | 20783 |
| | | | | | TEL | 128082 | 131263 | 125051 |

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|---|---|---|---|---|---|---|---|---|
| pPegRBVSVR | Probability of SVR with Peg +RBV | 0.41 | 0.36 | 0.46 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 23750 | 17924 |
| | | | | | BOC | 24234 | 27422 | 21589 |
| | | | | | TEL | 128082 | 134837 | 121947 |
| pRRBOCSVRnaive | RR of SVR with BOC in naive pop | 1.66 | 1.55 | 1.75 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 30388 | 20561 |
| | | | | | TEL | 128082 | 48738 | -718167 |
| pRRTelSVRnaive | Relative risk of SVR with Telaprevir in a naive pop | 1.69 | 1.58 | 1.78 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | -300322 | 55276 |
| pSE_PEGRBV | prob of anaemia Peg RBV | 0.285 | 0.15 | 0.43 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 19771 | 21372 |
| | | | | | BOC | 24234 | 25352 | 23073 |
| | | | | | TEL | 128082 | 128082 | 128082 |
| pTELRVR | probability of having an RVR with Telaprevir | 0.72 | 0.6 | 0.8 | NT | 0 | 0 | 0 |

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|---|---|---|---|---|---|---|---|---|
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 158811 | 111198 |
| pTransplantToDeath | prob of Death post-transplant without HCV | 0.02 | 0.01 | 0.05 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20505 | 20592 |
| | | | | | BOC | 24234 | 24201 | 24303 |
| | | | | | TEL | 128082 | 127984 | 128295 |
| pTransplantToDeathYr1 | prob of transplant to Death Yr1 (No HCV) | 0.14 | 0.12 | 0.2 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20527 | 20550 |
| | | | | | BOC | 24234 | 24227 | 24254 |
| | | | | | TEL | 128082 | 128062 | 128143 |
| startAge | starting age | 41.0 | 25 | 55 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 16748 | 31130 |
| | | | | | BOC | 24234 | 20333 | 34506 |
| | | | | | TEL | 128082 | 120696 | 142802 |
| (172) | Time Horizon | 50.0 | 20 | 60 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 42413 | 20353 |
| | | | | | BOC | 24234 | 44512 | 24051 |

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|---|---|---|---|---|---|---|---|---|
| | | | | | TEL | 128082 | 152895 | 127762 |
| uAnaemia | utility decrement from developing anaemia | 0.88 | 0.79 | 0.97 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20963 | 20119 |
| | | | | | BOC | 24234 | 24346 | 24122 |
| | | | | | TEL | 128082 | 119608 | 137848 |
| uCompCirr | Utility value for compensated cirrhosis | 0.64 | 0.52 | 0.76 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 18229 | 23502 |
| | | | | | BOC | 24234 | 21353 | 28013 |
| | | | | | TEL | 128082 | 126991 | 129192 |
| uDecomp | Utility value for Decompensated cirrhosis | 0.46 | 0.21 | 0.7 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 18904 | 22383 |
| | | | | | BOC | 24234 | 23330 | 25169 |
| | | | | | TEL | 128082 | 126181 | 129961 |
| uHCC | Utility value for HCC | 0.52 | 0.24 | 0.81 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20119 | 20979 |
| | | | | | BOC | 24234 | 23799 | 24700 |
| | | | | | TEL | 128082 | 127179 | 129031 |
| uMild | utility value of Mild healthstate | 0.75 | 0.71 | 0.79 | NT | 0 | 0 | 0 |

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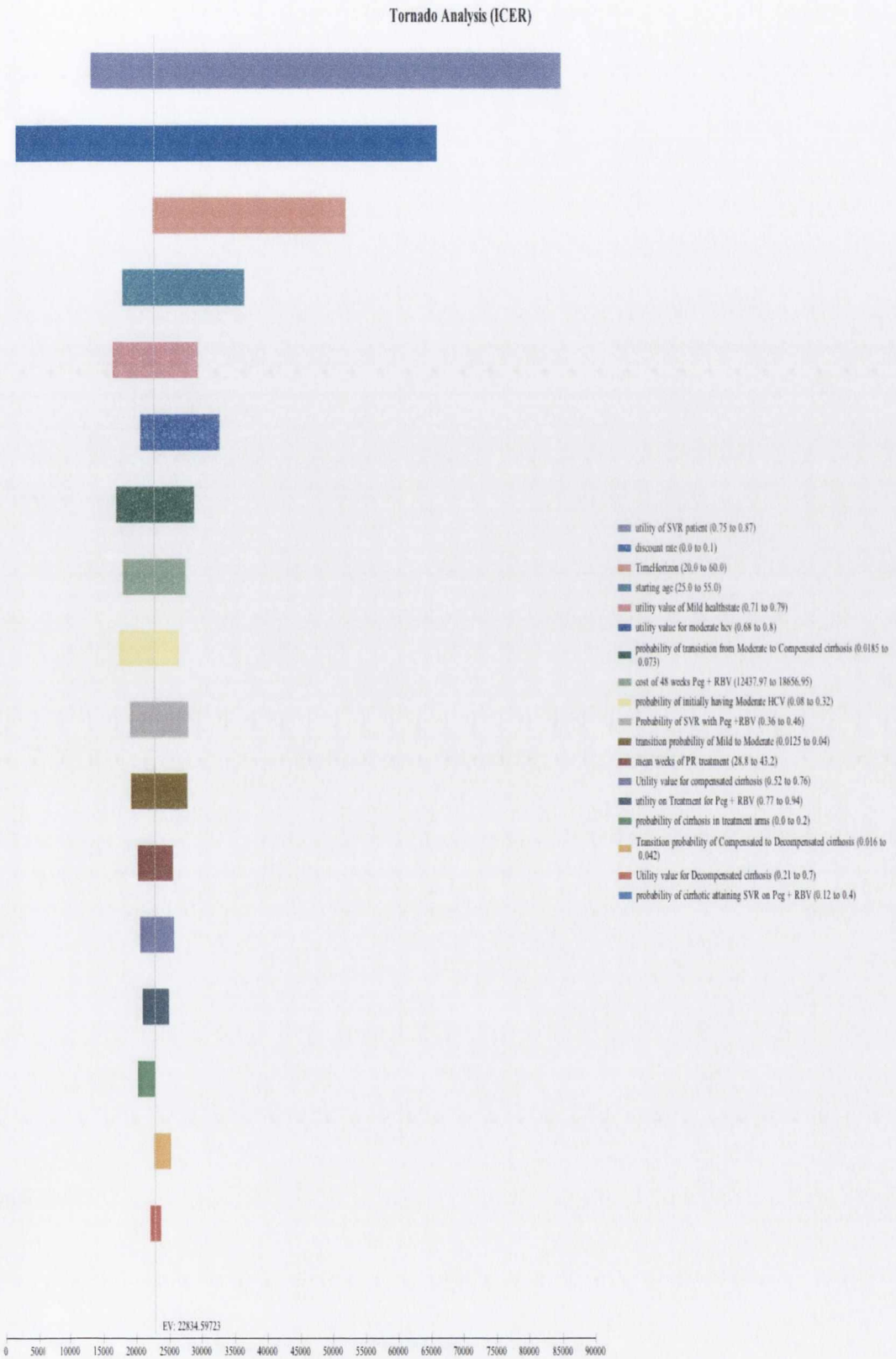
|---|---|---|---|---|---|---|---|---|
| | | | | | PR | 20533 | 16785 | 26433 |
| | | | | | BOC | 24234 | 20014 | 30708 |
| | | | | | TEL | 128082 | 123416 | 133115 |
| uModerate | utility value for moderate hcv | 0.74 | 0.68 | 0.8 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 17883 | 24103 |
| | | | | | BOC | 24234 | 21605 | 27590 |
| | | | | | TEL | 128082 | 120025 | 137299 |
| uPosttransplant | Utility for >1 year post-transplant | 0.59 | 0.52 | 0.67 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20542 | 20521 |
| | | | | | BOC | 24234 | 24243 | 24222 |
| | | | | | TEL | 128082 | 128103 | 128058 |
| uSVR | utility of SVR patient | 0.81 | 0.75 | 0.87 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 49330 | 12964 |
| | | | | | BOC | 24234 | 52566 | 15746 |
| | | | | | TEL | 128082 | 158966 | 107246 |
| uTransplant | Utility for Transplant 1st year | 0.49 | 0.24 | 0.75 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20514 | 20551 |
| | | | | | BOC | 24234 | 24214 | 24253 |
| | | | | | TEL | 128082 | 128042 | 128123 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| uTreatmentBOC | utility of on-treatment Boceprevir | 0.87 | 0.78 | 0.96 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 25647 | 22967 |
| | | | | | TEL | 128082 | 87010 | 242599 |
| uTreatmentPR | utility on Treatment for Peg + RBV | 0.85 | 0.77 | 0.94 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 22146 | 18977 |
| | | | | | BOC | 24234 | 23477 | 25144 |
| | | | | | TEL | 128082 | 127017 | 129032 |
| uTreatmentTel | Utility of Telaprevir on treatment | 0.86 | 0.77 | 0.95 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 20532 | 20532 |
| | | | | | BOC | 24234 | 24233 | 24233 |
| | | | | | TEL | 128082 | 160120 | 106727 |
| weeks_PR_before_Discontinue_TELnoRGT | mean weeks of PR treatment | 36.0 | 28.8 | 43.2 | NT | 0 | 0 | 0 |
| | | | | | PR | 20533 | 18204 | 22927 |
| | | | | | BOC | 24234 | 27542 | 21046 |
| | | | | | TEL | 128082 | 127033 | 129131 |
| Weeks_TEL_treatment | mean duration of telaprevir in those who discontinued | 10.7 | 8.56 | 12.8 | NT | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| | PR | 20533 | 20532 | 20532 |
| | BOC | 24234 | 24233 | 24233 |
| | TEL | 128082 | 110073 | 146624 |


Tornado Analysis (ICER)
utility of SVR patient (0.75 to 0.87)
discount rate (0.0 to 0.1)
TimeHorizon (20.0 to 60.0)
starting age (25.0 to 55.0)
utility value of Mild healthstate (0.71 to 0.79)
utility value for moderate hcv (0.68 to 0.8)
probability of transistion from Moderate to Compensated cirrhosis (0.0185 to 0.073)
cost of 48 weeks Peg + RBV (12437.97 to 18656.95)
probability of initially having Moderate HCV (0.08 to 0.32)
Probability of SVR with Peg +RBV (0.36 to 0.46)
transition probability of Mild to Moderate (0.0125 to 0.04)
mean weeks of PR treatment (28.8 to 43.2)
Utility value for compensated cirrhosis (0.52 to 0.76)
utility on Treatment for Peg + RBV (0.77 to 0.94)
probability of cirrhosis in treatment arms (0.0 to 0.2)
Transition probability of Compensated to Decompensated cirrhosis (0.016 to 0.042)
Utility value for Decompensated cirrhosis (0.21 to 0.7)
probability of cirrhotic attaining SVR on Peg + RBV (0.12 to 0.4)
EV: 22834.59723
0
5000
10000
15000
20000
25000
30000
35000
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60000
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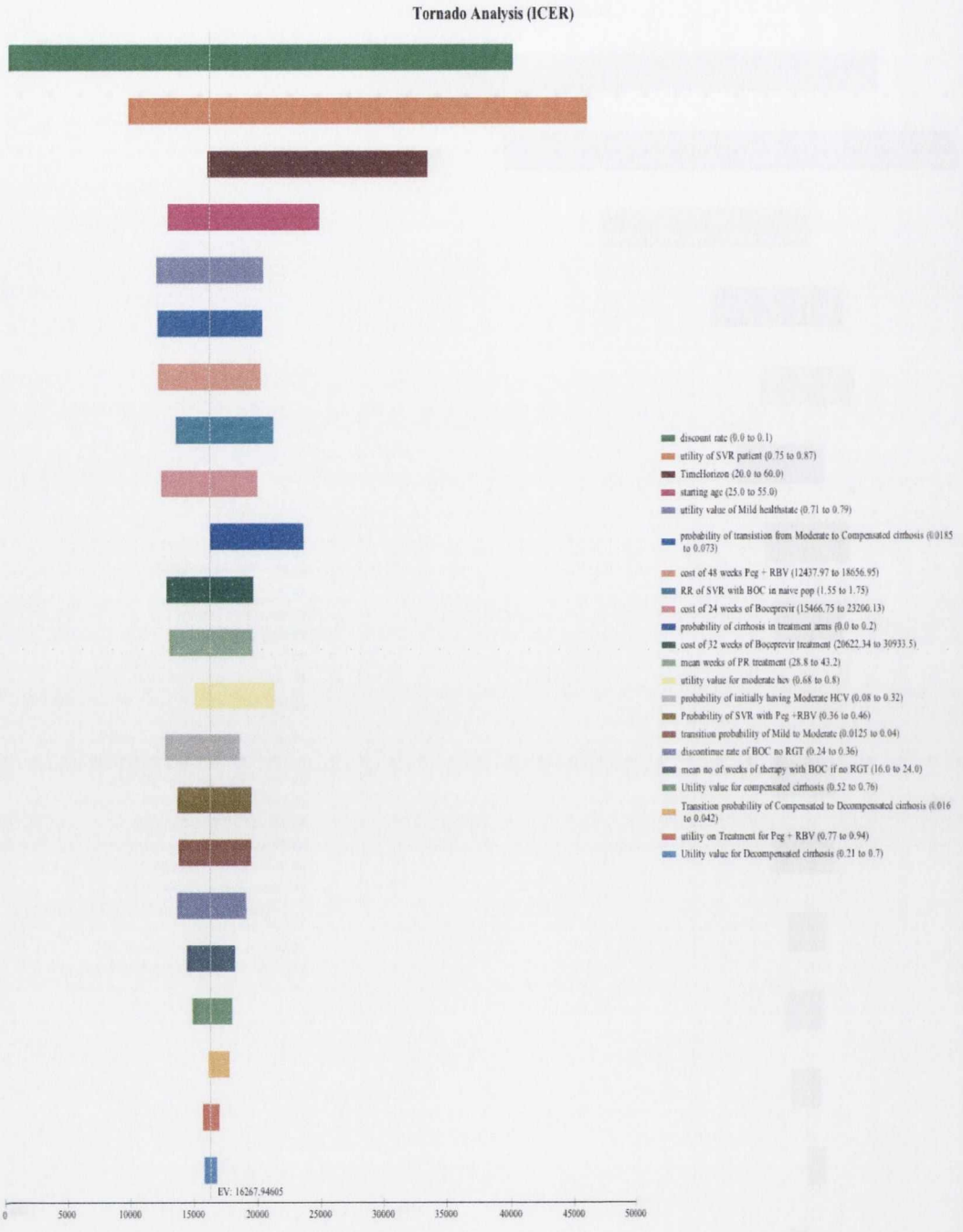
75000
80000
85000
90000


Tornado Analysis (ICER)
discount rate (0.0 to 0.1)
utility of SVR patient (0.75 to 0.87)
TimeHorizon (20.0 to 60.0)
starting age (25.0 to 55.0)
utility value of Mild healthstate (0.71 to 0.79)
probability of transistion from Moderate to Compensated cirrhosis (0.0185 to 0.073)
cost of 48 weeks Peg + RBV (12437.97 to 18656.95)
RR of SVR with BOC in naive pop (1.55 to 1.75)
cost of 24 weeks of Boceprevir (15466.75 to 23200.13)
probability of cirrhosis in treatment arms (0.0 to 0.2)
cost of 32 weeks of Boceprevir treatment (20622.34 to 30933.5)
mean weeks of PR treatment (28.8 to 43.2)
utility value for moderate hcv (0.68 to 0.8)
probability of initially having Moderate HCV (0.08 to 0.32)
Probability of SVR with Peg +RBV (0.36 to 0.46)
transition probability of Mild to Moderate (0.0125 to 0.04)
discontinue rate of BOC no RGT (0.24 to 0.36)
mean no of weeks of therapy with BOC if no RGT (16.0 to 24.0)
Utility value for compensated cirrhosis (0.52 to 0.76)
Transition probability of Compensated to Decompensated cirrhosis (0.016 to 0.042)
utility on Treatment for Peg + RBV (0.77 to 0.94)
Utility value for Decompensated cirrhosis (0.21 to 0.7)
EV: 16267.94605
0
5000
10000
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20000
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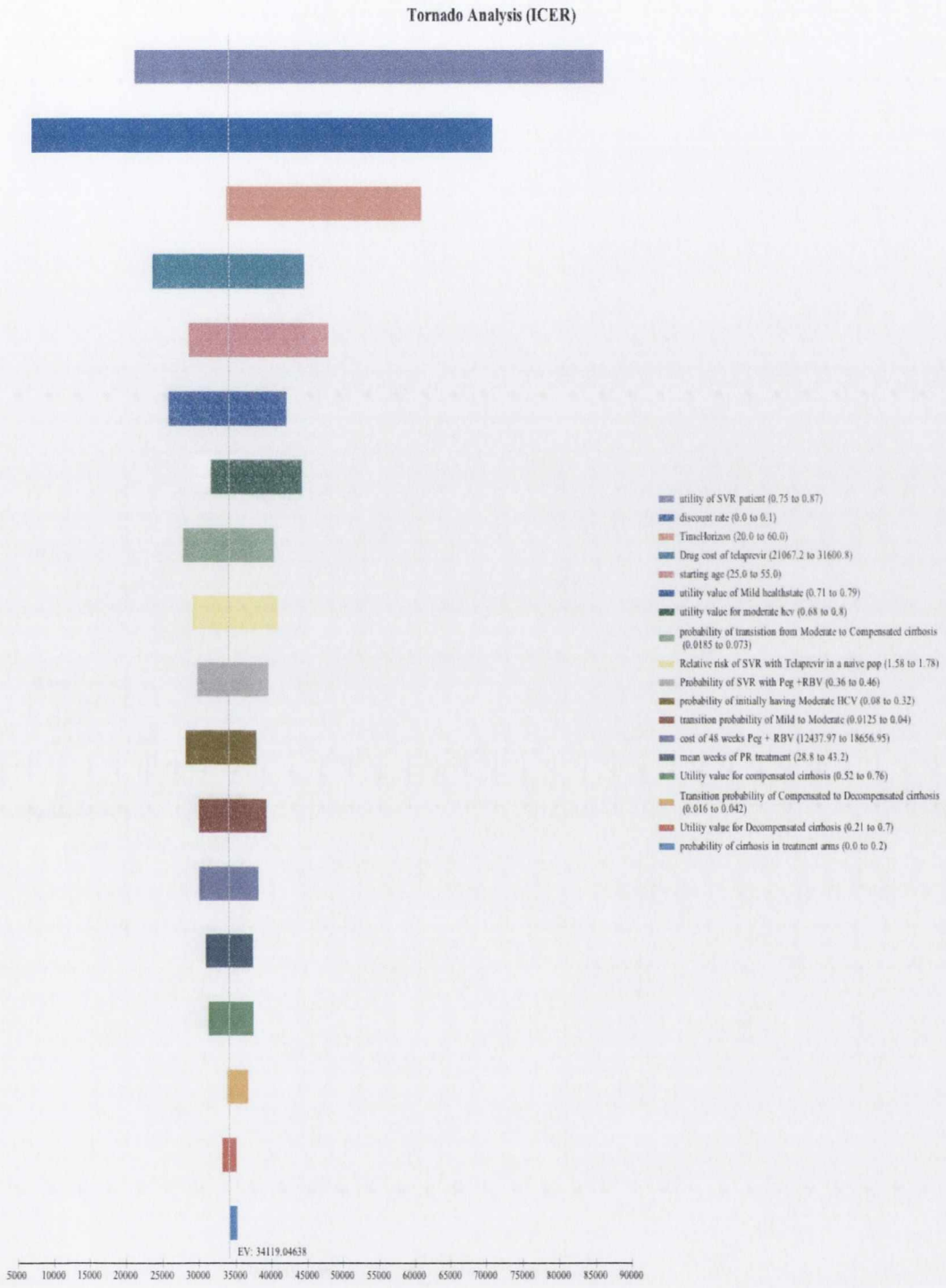
50000


Tornado Analysis (ICER)
utility of SVR patient (0.75 to 0.87)
discount rate (0.0 to 0.1)
TimeHorizon (20.0 to 60.0)
Drug cost of telaprevir (21067.2 to 31600.8)
starting age (25.0 to 55.0)
utility value of Mild healthstate (0.71 to 0.79)
utility value for moderate hcv (0.68 to 0.8)
probability of transistion from Moderate to Compensated cirrhosis (0.0185 to 0.073)
Relative risk of SVR with Telaprevir in a naive pop (1.58 to 1.78)
Probability of SVR with Peg +RBV (0.36 to 0.46)
probability of initially having Moderate HCV (0.08 to 0.32)
transition probability of Mild to Moderate (0.0125 to 0.04)
cost of 48 weeks Peg + RBV (12437.97 to 18656.95)
mean weeks of PR treatment (28.8 to 43.2)
Utility value for compensated cirrhosis (0.52 to 0.76)
Transition probability of Compensated to Decompensated cirrhosis (0.016 to 0.042)
Utility value for Decompensated cirrhosis (0.21 to 0.7)
probability of cirrhosis in treatment arms (0.0 to 0.2)
EV: 34119.04638
5000
10000
15000
20000
25000
30000
35000
40000
45000
50000
55000
60000
65000
70000
75000
80000
85000
90000

**Tornado Analysis (ICER)**

# References

# References

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