The Value of Real World Data in Healthcare Decision-Making: Practical Applications using Observational Data from the National Hepatitis C Treatment Registry

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Summary

Introduction Observational research can play an integral role in the healthcare decision-making process. In an era of ever increasing drug costs, healthcare decision-makers are under pressure to optimally allocate resources. It is essential they have access to a comprehensive evidence base to inform their decisions. Since the approval of the direct-acting antiviral (DAA) agents in Ireland in 2012, the hepatitis C (HCV) treatment landscape has been transformed. This was identified as an opportune time to maximise the therapeutic management of HCV infection in Ireland. Thus, the national HCV treatment registry was established. This thesis aims to utilise the registry to generate robust real world data to assess the impact of these regimens in the post-reimbursement era, and to demonstrate the value and practical application of observational data in healthcare decision-making.

Methods The registry utilises a prospective, longitudinal, observational cohort study. The effectiveness of the DAA regimens was established following analysis of the registry data. Micro-costing studies were undertaken to establish the cost of HCV-related healthcare for patients i) receiving DAA treatment ii) following premature discontinuation and iii) following achievement of a sustained virological response (SVR). Ambulatory care costs were compared with those of an untreated cohort. The perception, knowledge and attitudes to the registry among key stakeholders were determined through an online survey. A systematic literature review identified all published literature reporting the efficacy or effectiveness of licensed regimens for genotype (GT) 1 HCV-infected patients. This facilitated the comparison of our outcomes with other studies and informed a network meta-analysis (NMA) which aimed to assess the impact of including observational data in the estimation of the relative treatment effect of agents for the treatment of GT1 infection. We applied our effectiveness and cost data to an independently produced economic model and compared the output with the original analysis when RCT data and costs from other literature sources were inputted into the model.

Results SVR rates in the Irish clinical setting were comparable with the efficacy rates reported in RCTs when matched to similar patient populations, and our data generated real world data for subpopulations of patients excluded from these pivotal clinical trials. The SVR rates in the interferon (IFN)-free regimens (87%-90%) were higher than the SVR rates from IFN-based regimens (45%-74%). The mean per-patient cost of treatment with IFN-based regimens was €38,286 vs. €55,734 in IFN-free regimens primarily reflected by the higher drug acquisition costs for IFN-free regimens. Premature discontinuation was costly (€1,947 and €870 in those with and without cirrhosis, respectively). Following achievement of a SVR, patients with advanced cirrhosis continued to incur significant ambulatory costs attributable to the requirement for continued screening and higher risk of admission. The addition of observational data to the NMA did not have an impact on the relative treatment effect, potentially attributable to methodological issues. In the economic model, input parameters incorporating real world data had a significant impact on the cost-effectiveness of treatment regimens. The majority of key stakeholders (79%) were satisfied with their involvement in the HCV treatment registry, and the on-going monitoring of clinical and cost outcomes had practical implications in the management of patient undergoing treatment for HCV infection

Conclusion The generation and subsequent practical application of observational data derived from a treatment registry has demonstrated the value of such data for decision-makers in the Irish setting. It has had a direct impact on health policy in Ireland through its integral role in the establishment of the National Hepatitis C Clinical Programme and the on-going generation of robust real world data will be highly valuable to healthcare policy-makers, when incorporated with all other available evidence, as they continue to manage the budget impact of HCV infection in Ireland. This study indicates the feasibility of applying the methods and findings from this work to other high-cost therapeutic areas in Ireland.

Table of Contents

List of Figures

List of Tables

List of Publications

Peer-Reviewed Journal Articles

1. "Direct costs of interferon-based and interferon-free DAA regimens for the treatment of chronic hepatitis C infection", **Gray E,** O'Leary A, Kieran J, Fogarty E, Dowling T, Norris S. *Journal of Viral Hepatitis, (2016) 2016;23(9):677-86.*
2. "High mortality during direct acting antiviral therapy for hepatitis C patients with Child's C cirrhosis: Results from the Irish Early Access Programme" **Gray E,** O'Leary A, Norris S *et al* on behalf of the Irish Hepatitis C Outcomes Research Network *Journal of Hepatology 2016 Aug;65(2):446-8*
3. *"*Do disparities between populations in randomised controlled trials and the real world lead to differences in outcomes?" **Gray E,** O'Leary A, Schmitz S, Norris S, *Journal of Comparative Effectiveness Research, 2016 Nov 17 [Epub ahead of print]*
4. Effectiveness of triple therapy with direct-acting antivirals for hepatitis C genotype 1 infection: Application of propensity score matching in a national HCV treatment registry." **Gray E,** O'Leary A, Pasta D, Norris S, *BMC Health Services Research*
5. "Effectiveness of interferon-free therapy for the treatment of HCV-infected patients with compensated cirrhosis treated through the Irish EAP" **Gray E,** O'Leary A, Bergin C, Norris S *et al* on behalf of the Irish Hepatitis C Outcomes Research Network, *Expert Review of Gastroenterology and Hepatology, January 2017*

Oral Presentations

1. "Updates from the Irish national hepatitis C prospective treatment registry", Health Services Research and Pharmacy Practice Conference April 2015, Belfast, United Kingdom. Session: Pharmaceutical Public Health
2. "Outcomes from the Irish national Hepatitis C prospective treatment registry"**.** Irish Society of Gastroenterology (ISG) Winter Meeting December 2015, Dublin, Ireland (Awarded 2rd Prize)

Poster Presentations

1. "National HCV Treatment Outcomes of the DAA triple therapy cohort – first report of ICORN registry". **Gray, E,** O'Leary A, Walsh C, Bergin C, Norris S. ISGE Winter Meeting December 2013, Killarney, Ireland
2. "The ICORN Hepatitis C treatment registry – preliminary clinical and cost outcomes for triple therapy regimens". **Gray E,** O'Leary A, Bergin C, Norris S. Hospital Pharmacists Association of Ireland (HPAI) Conference April 2014, Dublin, Ireland.
3. "Outcomes from the Irish national hepatitis C prospective treatment registry". **Gray E**, O'Leary A, Walsh C, Bergin C, Norris S. Health Research Board (HRB) SPHeRE Network Annual Conference January 2015, Dublin.
1. "Resource Utilization in a Complex Treatment Regimen for Hepatitis C", **Gray E,** O'Leary A, Kieran J, Walsh C, Bergin C, Norris S. ISPOR 17th Annual European Congress, November 2014, Amsterdam, Holland.
2. "Outcomes from the Irish National Hepatitis C Prospective Treatment Registry", **Gray E,** O'Leary A, Walsh C, Bergin C, Norris S. The Liver Meeting 2014; 65th Annual Meeting of the American Association for the Study of Liver Diseases, November 2014, Boston, MA, USA.

3. “Estimation of the relative efficacy of licenced regimens for Genotype 1 HCV infection using a mixed treatment comparison”, **Gray E,** Leahy J, O’Leary A, Norris S, Walsh C. ISPOR 18th Annual European Congress, November 2015, Milan, Italy. Poster Presentation
4. “Real-world effectiveness of HCV infection from an Irish national HCV registry” **Gray E,** O’Leary A, Norris S *et al* on behalf of ICORN, International Conference on Pharmacoepidemiology and Risk Management, Dublin, August 2016
5. “Effectiveness of triple therapy with direct-acting antivirals for hepatitis C genotype 1 infection: Application of propensity score matching in a national HCV treatment registry” **Gray E,** O’Leary A, Pasta D, Norris S, International Conference on Pharmacoepidemiology and Risk Management, Dublin, August 2016

List of Abbreviations

3D±RBV	Paritaprevir, coformulated with low dose ritonavir and ombitasvir, administered with dasabuvir with or without ribavirin
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
BNF	British National Formulary
BOC	Boceprevir
BTD	Breakthrough therapy designation
CD81	Cluster of differentiation 81
CI	Confidence interval
CIDR	Computerised Infectious Disease Reporting
CLDN-1	Claudin-1
CNS	Clinical nurse specialist
CrI	Credible Interval
CTP	Child Turcotte Pugh
DAA	Direct-acting antiviral
DCCR	Dublin Centre for Clinical Research
DCV	Daclatasvir
DoH	Department of Health
DRG	Diagnostic Related Group
EAP	Early access program
EASL	European Association for the Study of Liver Diseases
EBM	Evidence based medicine
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPR	Electronic patient records
FDA	Food and Drugs Administration
GT	Genotype
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HLA	Human leukocyte antigen
HPSC	Health Protection Surveillance Centre
HRQoL	Health related quality of life

HSE	Health Service Executive
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICORN	Irish Hepatitis C Outcomes Research Network
IDSA	Infectious Disease Society of America
IFN	Interferon
IHI	Individual health identifier
IHNA	Irish Hepatology Nurses Association
IL28B	Interleukin 28B
IQR	Interquartile range
LD	Lipid droplets
LOR	Log odds ratio
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
MNAR	Missing not at random
MTC	Mixed treatment comparison
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NK	Natural killer
NMA	Network meta-analysis
NOS	Newcastle Ottawa Scale
NTR	Non-translated region
OCLN	Occludin
OR	Odd ratio
PCR	Polymerase chain reaction
PCRS	Primary Care Reimbursement Service
Peg-IFN	Pegylated-interferon
PI4KIIIa	Phosphatidylinositol 4 kinase IIIa
PR	Pegylated-interferon and ribavirin
PRISMA	Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses
PS	Propensity score
PWID	Persons who inject drugs
QALY	Quality adjusted life year
RBV	Ribavirin

RCT	Randomised controlled trial
RNA	Ribonucleic acid
SMV	Simeprevir
SNP	Single nucleotide polymorphism
SOF	Sofosbuvir
SOF/DCV±RBV	Sofosbuvir and daclatasvir with or without ribavirin
SOF/LDV±RBV	Sofosbuvir with ledipasvir with or without ribavirin
SOF/SMV±RBV	Sofosbuvir with simeprevir with or without ribavirin
SOF±RBV	Sofosbuvir with or without ribavirin
SPC	Summary of Product Characteristics
SRB1	Scavenger receptor class B type I
SUCRA	Surface area under the cumulative rankogram curve
SVR	Sustained virological response
SVR12	Sustained virological response 12 weeks post-treatment
SVR24	Sustained virological response 24 weeks post-treatment
TPV	Telaprevir
VA	Veteran Affairs
WHO	World Health Organisation
WTP	Willingness-to-pay

Chapter 1

Chapter 1 Introduction

Infection with the hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease [1]. It is estimated to affect >185 million people, with a prevalence of approximately 3% in the worldwide population [2-4]. In Ireland, HCV is estimated to affect between 20,000 and 50,000 people [5]. Over the last twenty years, treatment for HCV has evolved rapidly. Since 2011, with the availability of the direct-acting antiviral (DAA) agents for use with, and subsequently, without pegylated-interferon and ribavirin (PR), the treatment landscape for HCV infection has evolved rapidly [6, 7].

Given the high drug acquisition cost of these DAA agents, epidemiological data indicates the budget impact of treating the HCV-infected cohort in Ireland to be significant and raises the question of affordability. In the current era of ever-increasing drug costs, methods are required to determine the most cost-effective treatments for patients [8]. In 2012 it was recognized in Ireland that robust real world data was needed to best understand the effectiveness and benefits of these new treatments. Thus, policy-makers recommended the establishment of a national HCV registry, which would determine the real world impact of these regimens.

The potential for registries in collecting real world data is substantial [9]. However, there is an on-going debate about the value of using this observational evidence either in the absence of randomised evidence or as an adjunct to it [10]. While considered the 'gold' standard in the hierarchy of research designs for evaluating the efficacy and safety of treatment interventions, the value of relying solely on randomised clinical trials (RCTs) for estimating treatment effectiveness is limited by their lack of generalisability, their short duration, the lack of follow-up and small sample sizes [11-13]. Observational data is becoming increasingly recognised as an important component of the evidence that can

provide valuable information regarding the effectiveness and appropriate use of agents in the real world, outside of clinical trials [14, 15]. Decision-makers should endeavour to assess and appraise all the available sources of evidence, whether derived from randomised controlled trials (RCTs) or observational research, at the time of reimbursement and during the post-reimbursement era. A comprehensive evidence base, including both RCTs and high-quality, well-designed observational studies, is important when making balanced judgments about the management of diseases and selecting appropriate treatments that provide optimal value [11, 13]. Real world data can provide useful information to enhance robust reimbursement decisions. Healthcare decision-makers responsible for reimbursement decisions are increasingly seeking such real world outcome and cost data to inform their decisions [16].

1.1 Aims and Objectives

The aim of this thesis is to generate robust real world data that can be used to assess the impact of DAA regimens in the post-reimbursement era and demonstrate the value and practical application of observational data in healthcare decision-making using data from the Irish national HCV treatment registry.

The objectives are as follows:

- To undertake a systematic literature review to identify the published literature reporting the rates of efficacy and effectiveness of DAA treatment regimens licensed for use in patients infected with genotype 1 HCV infection in RCTs and observational studies and to compare the outcomes between the two study types.
- To establish the effectiveness of the new treatments for HCV infection in the Irish clinical setting and to apply appropriate statistical analytical techniques to deal with the limitations associated with observational data.

- To determine the HCV-related healthcare cost of treating HCV infection with DAA agents in a hospital-based ambulatory care setting in Ireland. Additionally, the mean annual cost of premature discontinuation following virological failure, adverse event, non-compliance or other miscellaneous reasons will be estimated.
- To determine if achieving a sustained virological response (SVR) resulted in decreased or increased mean annual HCV-related healthcare costs and the factors influencing these costs in the post-SVR era.
- To determine the attitudes and perceptions of Irish healthcare stakeholders to the national HCV treatment registry.
- To examine the practical value of observational data by assessing the impact of including observational data in a network meta-analysis and incorporating our real world efficacy rates and cost estimations into a economic model.

1.2 Overview of Chapters 2 to 9

Chapter 2 and Chapter 3 provide background information for this thesis. Chapter 2 provides comprehensive information on HCV including basic virology, the epidemiology of HCV, the HCV landscape in Ireland and the treatment options available. Chapter 3 introduces the concept of observational research including the different types of observational studies, their advantages and limitations with particular focus on registries. This chapter also provides information on evidence synthesis including meta-analysis and network meta-analysis and it is completed with information on the establishment of the Irish national HCV treatment registry in 2012.

Chapters 4 to 7 present the original research of this thesis. Chapter 4 presents the systematic literature review that identified all published literature that reported the

efficacy or effectiveness of licensed regimens for genotype 1 HCV-infected patients. In this study, we compared the SVR rates between RCTs and observational studies and investigated possible reasons for disparities in outcomes between the two study types. Chapter 5 presents the effectiveness rates for interferon (IFN)-based and IFN-free regimens in the Irish settings using the data from the Irish national HCV treatment registry. We reported data for three cohorts of patients; applying propensity scoring, where appropriate, to deal with the issue of confounding bias, a common limitation associated with observational research. Chapter 6 presents the results of the costing studies undertaken to establish the cost of treating HCV infection with DAA agents in the Irish setting and estimated the mean annual cost of premature discontinuation of IFN-based treatment following virological failure, adverse events, non-compliance or other miscellaneous reasons. Additionally, this chapter presents the results of a study undertaken to determine if achieving a SVR resulted in an increase or decrease in mean annual HCV-related healthcare costs when compared with the costs established previously for untreated HCV infection. Chapter 7 presents the findings from a quantitative survey of the attitudes and perceptions of physicians, nurses and other key stakeholders to the HCV registry.

Chapter 8 utilised the results from these studies to demonstrate the practical application of observational data in outcomes research. In this chapter, we examined the impact of including effectiveness rates from observational studies to assess the relative treatment effect for all treatment regimens licensed for use in genotype 1 HCV infected-patients. Additionally, the effectiveness rates and costs established in this thesis were incorporated into an independently developed economic model, which aimed to address the question of cost effectiveness of HCV treatments in Ireland. We assessed the impact of using real world data in the model and compared these results

with the output from the original analysis which incorporated efficacy rates from RCTs and costs from list prices.

Chapter 9 is the concluding chapter where a summary of the main findings, their impact on health policy and the implication of the outcomes for the future are presented.

1.3 Conclusion

Observational data can provide valuable information regarding the effectiveness and appropriate use of agents in the real world, outside of clinical trials. Determining Irish values for effectiveness and HCV-related costs provide robust real world data fundamental for input into future economic evaluations for agents used in the treatment of HCV infection. Understanding the value of these data and incorporating it into the evidence network are essential for those with responsibility for making sound decisions regarding coverage and reimbursement.

While this research focuses on the area of HCV infection, by demonstrating the value of generating real world data for healthcare decision-making, we envisage that policy-makers in other disease areas would benefit from establishing similar national registries and utilising the methodologies employed in the studies presented in this thesis. As demonstrated by the findings from this study, the determination of robust, country-specific, real world data will enhance the evidence assessed and appraised by healthcare decision-making for the appropriate allocation of limited resources.

Chapter 2

Chapter 2 Hepatitis C and Treatment in the Irish Setting

2.1 Virology

The discovery of HCV was the direct result of the landmark discoveries of hepatitis B virus and hepatitis A virus and their serologies [17]. HCV was originally cloned in 1989 as the causative agent of non-A, non-B hepatitis [18, 19]. It is a single-stranded positive ribonucleic acid (RNA) virus that belongs to the flaviviridae family, approximately 9600 nucleotides in length. The viral genome encodes a single precursor polyprotein of approximately 3000 amino acids. This is cleaved by viral and cellular proteases into a number of viral proteins [20]. It has been estimated that chronically infected individuals replicate 10^{12} virions per day [21]. The HCV virion is comprised of a nucleocapsid core surrounded by a host-derived lipid membrane which consist of the envelope glycoprotein, E1 and E2 [22]. Until recently, the exact nature of the HCV virology and life cycle was poorly understood and further research was required to understand the exact nature of this life cycle. The results from this research into the elucidation of the virology have led to significant advances in treatment over the last 5 years.

2.1.1 Life Cycle

Figure 1 identifies the seven steps in the HCV life cycle that can also serve as targets for potential novel therapeutic agents. Every step of the life cycle offers a variety of potential targets for novel therapeutics.

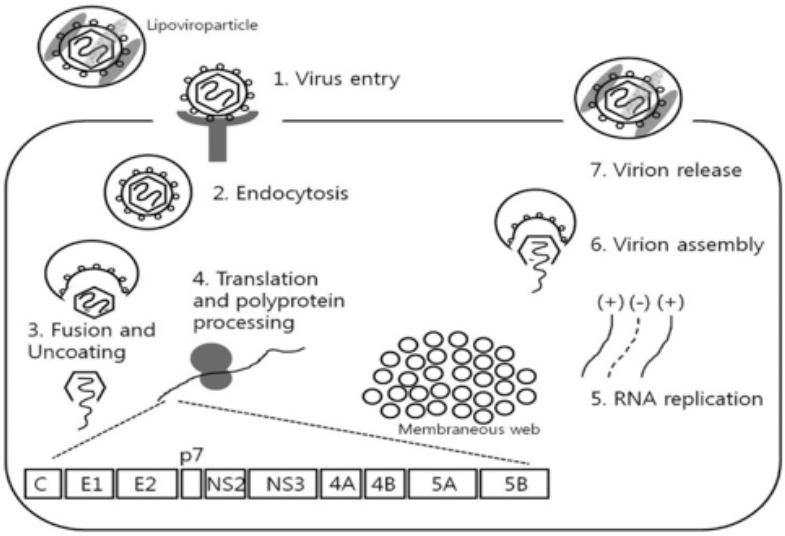


Figure 1: Schematic representation of the HCV life cycle
Sourced from Kim et al [19]

Viral entry is initiated by binding to an attachment factor present at the plasma membrane of the target cell, the hepatocyte [21]. The envelope glycoproteins are the major determinants of HCV entry. They play a role in receptor binding, and mediate the fusion process between the viral envelope and an endosomal host cell membrane [23]. E1 and E2 proteins interact with specific receptors on the surface of hepatocytes, which actively promote virus entry by inducing conformational changes of the viral particle or by activating signalling pathways or internalisation of the virion. Multiple cellular receptors have been identified including scavenger receptor class B type 1 (SRB1) and cluster of differentiation 81 (CD81), as well as the tight junction proteins claudin-1 (CLDN-1) and occludin (OCLN) [19, 21-23]. While the exact nature of their role is not completely understood, it is likely that they facilitate a change in the E1/E2 envelope glycoprotein that promotes fusion and viral endocytosis.

After attachment, the nucleocapsid of enveloped viruses is released into the cell cytoplasm as a result of the fusion process between viral and cellular membranes. Fusion is mediated by specialised viral proteins and takes place either directly at the plasma membrane or following internalisation of the particles into endosomes. The

entry process is controlled by viral surface glycoproteins that trigger the changes required for mediating fusion [24]. Following entry into hepatocytes through receptor-mediated endocytosis, HCV particles undergo pH-dependent membrane fusion within an acidic endosomal compartment to release its RNA genome into the cytoplasm.

Translation occurs in the cytoplasm and is initiated with the help of cellular factors. The HCV genome contains a single open reading frame flanked by 5' and 3' non-translated regions (NTRs), which contain highly structured RNA elements that are critical for genome translation and HCV RNA replication. The 5' NTR contains an internal ribosome entry site which initiates translation of the HCV genome into a single polyprotein [23, 24]. Viral and host proteases process the viral polyprotein into 10 mature proteins, the three structural proteins (core, E1 and E2), a small protein p7 which is required for viral assembly and release and six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B). The non-structural proteins collectively contribute to various aspect of the HCV life cycle including viral attachment, entry and fusion, HCV-RNA translation, post-translational processing, HCV replication, virus assembly and release [19, 23, 24].

Infection with the HCV-RNA virus leads to rearrangement of intracellular membranes and induces the formation of a 'membranous web' that is derived from endoplasmic reticulum membranes. Viral replication occurs at this site with the non-structural proteins playing a vital role. NS3 through NS5B comprise the replication machinery, which replicates the positive sense RNA genome through a negative strand intermediate to produce new viral proteins which are assembled into infectious virions [21]. Various cellular factors are involved in HCV replication, including cyclophilin A and phosphatidylinositol 4 kinase IIIα (PI4KIIIα). Cyclophilin A modulates RNA-binding capacity of NS5B and interacts with NS5A while PI4KIIIα is recruited to the

'membranous web' by NS5A and thus both play critical roles in the viral replication process [19, 23, 24].

Little is understood about HCV viral assembly and release. It appears that HCV virus assembly requires close interaction with lipid droplets and lipoprotein particles. HCV infection induces a profound change in the intracellular distribution of lipid droplets (LDs). LDs play a central role in HCV assembly since the viral proteins and viral genome are in close proximity. Additionally, the HCV core protein plays an essential role in this process since it directly interacts with LDs. Some non-structural proteins such as NS5A and NS3 are also found around LDs in HCV-infected cells. The core-LD association is essential for virus production. Importantly, NS5A emerges as a central element in the transition between replication and assembly. It is likely that all other viral proteins play a key role in the assembly process, centring on lipid droplets where assembly is triggered in the membranous and lipid-rich environment by the structural HCV proteins and the replication complex. Following accumulation of all the viral components close to the LDs, virion assembly is facilitated. This process can be divided into three steps: nucleocapsid formation, budding and maturation to the infectious particle [19, 21, 23, 25]. After assembly and budding in the endoplasmic reticulum, the virus appears to be released through the secretory pathway in association with distinct lipid and apolipoprotein associations.

2.1.2 Immune Response to HCV Infection

The inefficiency of the immune system in eliminating this virus is not well understood. Effective clearance of an acute viral infection typically requires the coordinated function of multiple arms of the immune system, including the innate immune system (IFNs, natural killer (NK) and NK T-cells), as well as the adaptive or acquired immune response specific to a given pathogen ($CD4^+$ and $CD8^+$) [26]. Successful clearance of

HCV infection requires activation of NK cells, which is followed by a cascade of events leading to the production of IFN-γ. IFN triggers the innate cellular antiviral response, which functions to limit viral replication [27, 28]. The mechanism by which chronic HCV develops and persists in the majority of infected individuals remains unclear, but it does so despite the presence of HCV-specific $CD4^+$ and $CD8^+$ T-cell responses in the peripheral blood and the liver, which suggests that these responses are, for the most part, ineffective [26].

2.2 Acute Hepatitis C

Acute infection with HCV is often unrecognised because individuals are commonly asymptomatic. HCV infection is diagnosed by anti-HCV testing. Antibodies against HCV are present during all stages of the infection and for some time after viral clearance. However, diagnosis in the acute phase is difficult because this production of antibodies can be delayed by up to 12 weeks following exposure. As serum HCV-RNA becomes detectable 1-3 weeks following exposure, HCV-RNA testing by polymerase chain reaction (PCR) is the only reliable test for the accurate diagnosis of acute infection [29, 30]. Other criteria considered when diagnosing patients include an acute increase in alanine aminotransferase (ALT) levels to >10 times above the normal upper limit and the potential for exposure to HCV during the previous 2-12 weeks [31]. The identification of treatments for acute HCV was hindered by the difficulties in its diagnosis. However, clinical trials have investigated treatment for acute infection with a 24-week course of standard IFN-α monotherapy and reported SVR rates in the range of 71%-94% [30, 32]. The rate of spontaneous clearance after acute HCV infection is conservatively estimated to be 15%–25% [28]. Host and viral factors including ethnicity, gender, race, presence or absence of specific human leukocyte antigen (HLA) type II alleles, HCV genotype and the strength and pattern of HCV-specific CD4 cell responses are proposed as being associated with spontaneous viral clearance [31, 33].

2.3 Chronic Hepatitis C

Chronic hepatitis C is defined as persistent, detectable serum HCV-RNA levels, for a period greater than 6 months, with or without liver function test abnormalities [34]. Persistence of HCV infection results when innate responses are blunted, thus dampening the priming of adaptive responses. T-cell induction of IFN-γ clears HCV infection, while a poor response to IFN-γ permits continued viral replication with its effect on cytokine release [28]. As previously stated, between 75% and 85% of those infected with acute hepatitis C will go on to develop a chronic condition.

2.3.1 Progression

Globally, hepatitis B is the leading cause of liver failure, hepatocellular carcinoma (HCC) and one of the most common reason for liver transplantation worldwide [35]. However, in Western countries, chronic hepatitis C is the leading indication for liver failure and subsequent transplantation [36]. Disease progression is exceedingly slow. Both host and viral factors are considered to play a role in disease progression. These include age, duration of infection, gender, race, viral concentration and genotype [28, 37, 38]. The end-stage consequence of fibrosis progression is cirrhosis, and if untreated, can lead to hepatic decompensation and the development of HCC [37, 39]. A meta-analysis by *Thein et al* calculated that cirrhosis developed, on average, in 16% of patients within 20 years of onset of HCV [40]. This figure can vary from between 14-62% and is explained by regional differences and other co-factors associated with fibrosis progression [37, 40-42]. Once cirrhosis develops, outcomes typical of advanced liver disease, or decompensation, may occur, including ascites, variceal bleeding and hepatic encephalopathy, leading to transplantation or death [43]. An estimated 25% of HCC can be attributed to HCV and up to 7% of cirrhotic patients can develop HCC [44, 45]. Up to 80% of those with HCC will die each year [45-48]. Although the incidence of new HCV infections is declining, particularly in developed countries, without adequate

treatment the morbidity and mortality associated with HCV infection will continue to increase. Both the longstanding nature of the infection and an ageing population is contributing to a significant increase in HCV-related cirrhosis and premature deaths in recent times [2, 49].

2.4 Genotype

HCV exhibits an extraordinarily high degree of genetic diversity. HCV is classified into at least seven recognised genotypes (GT) (1-7) on the basis of phylogenetic and sequence analyses of whole viral genomes. HCV strains belonging to different genotypes differ at 30%-35% of nucleotide sites. Within each genotype, HCV is further classified into over 50 subtypes. Strains that belong to the same subtype differ at <15% of nucleotide sites [3, 50].

It has been established that a few subtypes, specifically 1a, 1b, 2a and 3a, are widely distributed across the globe and account for a large proportion of HCV infections in developed countries [3]. GT1 is the most common cause of HCV infection worldwide, accounting for 46% of all infections. The prevalence of other genotypes is lower. GT3 accounts for 22%, GT2 for 13% and GT4 for 13% of all infections [51, 52]. However, significant geographic variation exists. GT1 is dominant in Australasia, Europe, Latin American and North America (53%-71% of all cases) while GT3 accounts for 40% of all infections in Asia. In North Africa and the Middle East, GT4 is most common (71%) [51]. GT1, the most prevalent genotype in Europe, and Ireland, is composed of at least 60 subtypes with differences in nucleotide and amino acid sequences. HCV subtypes 1a and 1b are the major strains and show geographical variation, with subtype 1a the most prevalent in Europe [53]. Certain genotypes are easier to treat and, thus, the recommended drug therapy and duration of treatment varies by genotype. For this

reason, determination of an infected individual's genotype is important to appropriately tailor therapy [52].

2.5 Routes of Transmission

The most efficient transmission of HCV is through large or repeated direct percutaneous exposure to blood [54]. HCV is less efficiently transmitted by single small dose percutaneous exposures. Risk factors associated with acquiring infection include transfusion of blood or blood products, injecting drug use, unsafe therapeutic injections, occupational exposure to blood, birth to an infected mother, sex with an infected partner and sex with multiple partners. Epidemiological studies on the role of potential risk factors, such as medical procedures, injections for medications and immunisations, injecting drug use, tattoos and in a minority of cases, sexual transmission, have shown wide geographical variations [55]. In developed countries, the prevalence of anti-HCV among persons who inject drugs (PWID) ranges from 31%-98% [56]. In developing countries, HCV transmission is mainly by contaminated blood products.

2.6 Epidemiology

It is now well established that HCV is of global importance and presents significant disease burden [52]. The World Health Organisation (WHO) declared HCV a global health problem due to its impact on morbidity and mortality. Only a small proportion of those infected receive antiviral treatment, and up to half of those are unaware of this infection. Reasons for this include lack of awareness and knowledge of HCV among healthcare providers, at-risk patients, health policy-makers and the public. This contributes to poor screening services and missed opportunities for diagnosis, prevention and treatment [43].

In 2010, the Global Burden of Diseases, Injuries and Risk Factors study was undertaken to estimate the burden of HCV infection [4]. Since 1990, the numbers with HCV antibodies has risen from 122 million to over 185 millions. The prevalence of HCV demonstrates considerable geographical variation, which may be explained by different distributions and different contributions of risk factors in different study regions (Table 1) [4, 51]. Although prevalence is highest in Egypt, China has the most infected individuals with 29.8 million [57].

Table 1: Example of the variation in the global prevalence of HCV-RNA

Country	Viraemic Prevalence (%)
Asia	
Japan	1.1
China	0.8
Pakistan	5.8
Australasia	
Australia	1.2
Europe	
Romania	2.9
United Kingdom	0.4
Ireland	0.8
Italy	1.5
Latvia	1.7
Africa	
Egypt	10
Morocco	1.1
Latin America	
Brazil	1.3
North America	
United States	1

A recent study in Europe estimated that the prevalence of HCV varies between 2.4% for Western and Central Europe and 2.9% for Eastern Europe. With a global population of 740 million, it is estimated that the pool of HCV infected individuals in Europe is 19 million [58].

2.6.1 HCV in Ireland

In Ireland, HCV is recognised as a significant public health problem yet the prevalence is poorly characterised. It is likely that there are many infected patients whom remain undiagnosed. HCV became a notifiable disease in Ireland in 2004. Cases are reported to the Health Protection Surveillance Centre (HPSC) through the Computerised Infectious Disease Reporting (CIDR) system. There have been over 14,000 cases of HCV notified in the 10 year period between 2004 and 2014 [59]. The number of cases notified reached a peak in 2007 and has steadily declined since with 710 cases notified in 2014 (Figure 2).

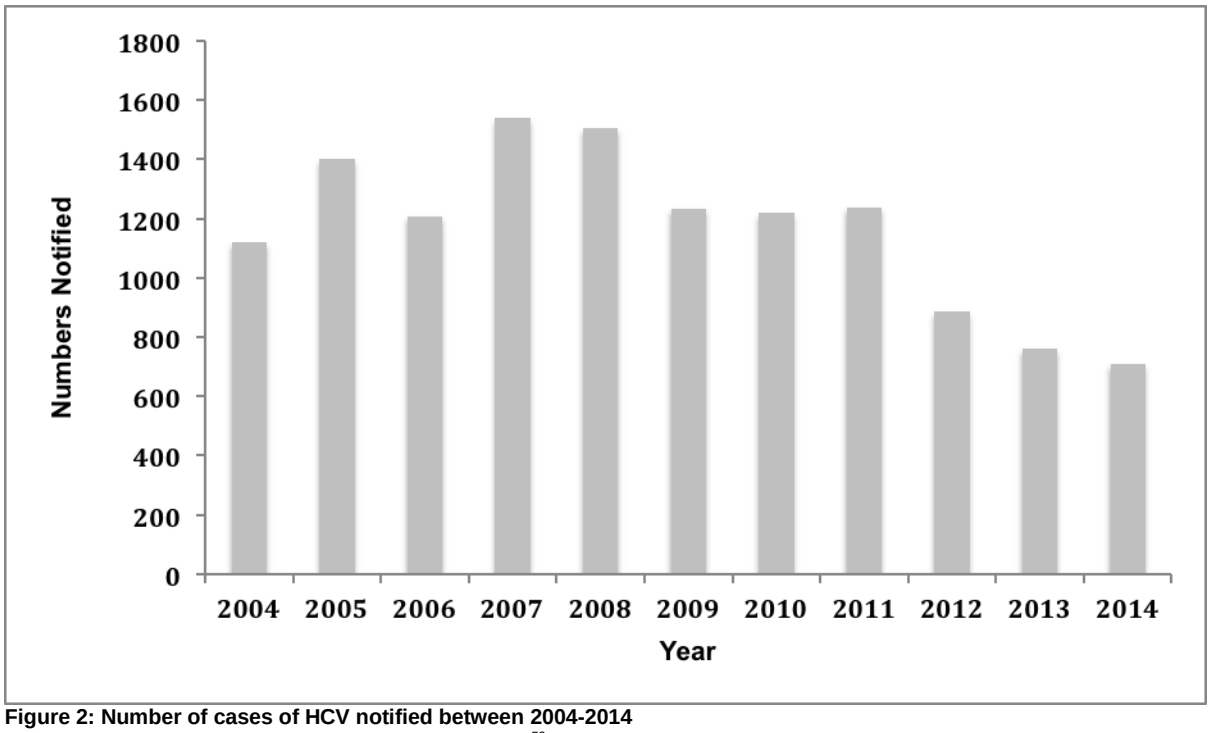


Figure 2: Number of cases of HCV notified between 2004-2014
Sourced from the Health Protection Surveillance Centre[59]

A collaborative study between the HSPC and the National Virus Reference Laboratory (NVRL) to estimate the prevalence of the infection in Ireland was published in 2012 [5]. Specimen-based laboratory data, for the period of 1989-2004, was translated to person-based data and combined with notification data from 2004-2009. From this, it was estimated that some 20,000-50,000 people in Ireland are chronically infected with

HCV, which equates to a population prevalence of 0·5-1·2%, with the majority yet to be diagnosed. This was similar to the prevalence estimates in other Northern European countries. However, these estimates are subject to uncertainty and the true prevalence rate of HCV in Ireland is unknown. This study also estimated the genotype profile of HCV-infected patients and it was established that GT1 accounted for 55% of HCV infections in Ireland [5]. GT3 accounted for 39%, 4% were GT2 and 1% were GT4.

The main causes of HCV in Ireland are injecting drug use and receipt of contaminated blood or blood products [5]. Studies in Ireland among PWIDs, between 1992 and 2006, reported a HCV antibody prevalence of between 52-84% [60-66].

2.6.1.1 Irish Legacy Cohort

October 1991 saw the commencement of routine screening for HCV antibodies in blood donors in Ireland [67]. A regional study of donors completed in early 1994 identified 14 men and 15 women with HCV antibodies. It was noted that the 15 women differed substantially from the overall donor population. These women were older and 87% were Rh-negative, compared to 18% in the general population. Administration of anti-D immune globulin to Rh (D) negative women who have delivered Rh (D) positive babies is a vital part of obstetric care. Twelve of these women had received anti-D immune globulin in 1977. Subsequent analysis of batches of anti-D immune globulin, used in Ireland to prevent Rh isoimmunisation was found to be contaminated with HCV (GT1b) from a single infected donor [67].

This led to the initiation of a national screening programme for people who had received blood or blood products prior to the introduction of routine HCV antibody screening of blood-product donors in October 1991. In total, over 62,000 women

presented for screening. Of these, 704 had evidence of past or current infection with HCV and 390 tested positive for serum HCV RNA [67]. All of these women were referred to one of six hepatology centres throughout the country.

A second outbreak of HCV virus occurred between 1991 and 1994 as a result of administration of IV anti-D immune globulin batches manufactured in Ireland [68]. A total of 44 women exposed to these batches of immune globulin were positive for HCV-RNA. Overall, approximately 1700 people infected with HCV through blood or blood products have been identified.

2.7 Burden of Disease

As previously discussed, persistent HCV infection may lead to progressive liver disease with the development of liver cirrhosis and HCC, accounting for up to 0.5 million deaths, worldwide, per year [69]. A study published in 2015 by Sibley *et al* [70] illustrated that the total number of new HCV infections is projected to decline due to a combination of an ageing prevalent population, treatment and a reduction in risk factors due to improvements in screening of blood products and harm reduction programmes of PWIDs. However, morbidity and mortality attributable to HCV are expected to increase as the current population progresses to advanced stages of liver disease. Data from the Centre for Disease Control (CDC) estimate that there are 12,000 deaths from HCV in the US per year [71]. Studies have demonstrated that for almost all countries, the peak of HCV-related cirrhosis, HCC and liver-related death is a decade or more away [70, 72-76]. A consistent finding was that a reduction in HCV liver-related mortality is dependent on access to therapy. Increasing efficacy of therapy alone with a constant number of treatments will not have a major impact on HCV-related disease burden. Reducing HCV disease burden is possible with a two-pronged effort, where active screening programmes find and identify HCV-infected individuals and where

active management with antiviral therapy is maintained [72]. Highly effective, oral DAAs offer a new hope to reduce the disease burden of HCV. However, to maximise the benefits of new DAAs, expanded screening and substantial expansion in treatment capacity are necessary in the near term. Without these changes, the HCV burden will remain substantial [77].

In 2011, Razavi *et al* estimated the total cost associated with HCV disease burden in the US to be USD$6.5 billion (€5.6 billion) [78]. This is expected to peak in 2024 at USD$9.1 billion (€7.9 billion). The estimated lifetime healthcare costs associated with HCV-infected individuals in 2011 were in the region of USD$64,000 (~€55,500). However, as life expectancy increases, this cost will also rise. Similarly, in a study be Myer *et al*, the total costs associated with HCV in Canada are projected to increase from CAD$161 million (€109 million) in 2013 to CAD$258 million (€175 million) at its peak in 2032. The estimated lifetime costs are CAD$64,700 (~€44,000) but range from CAD$51,946 (~€35,500) for an individual with no fibrosis (F0) to CAD$327,608 (~€224,000) for an individual requiring a liver transplantation. In the UK, it was projected that healthcare costs would increase from £82.7 million (€104 million) in 2012 to £115 million (€145 million) in 2035 [79]. It is clear that, in addition to the morbidity and mortality associated with the infection, HCV presents a significant cost burden that is expected to increase in the absence of improvement in screening programmes, capacity to treat and efficacy of treatments.

In Ireland, given that PWIDs play a significant role in HCV transmission, the age of the HCV-infected population is relatively young. As a result, it has been predicted that much of the burden of HCV-related morbidity and mortality will occur after 2030 [73]. Increases in the treatment efficacy and the annual treated population have the potential to greatly impact the burden of disease in Ireland. Compared to other countries, Ireland

has relatively few individuals who have progressed to cirrhosis or advanced liver disease but evidence of the increase in incidence of HCC suggests that the numbers with advanced liver disease is growing (Figure 3) [80].

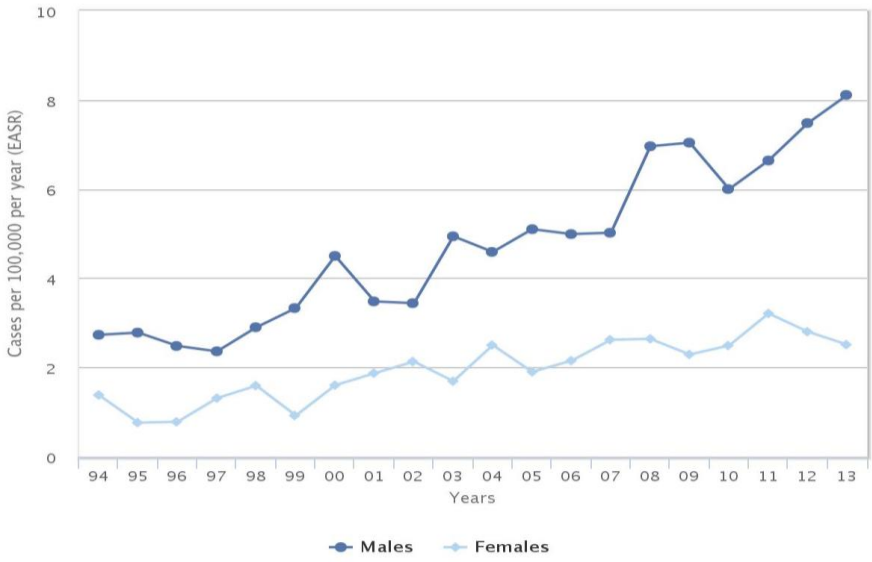


Figure 3: Incidence of hepatocellular carcinoma from 1994-2013 in both males and females.
Sourced from the National Cancer Registry Ireland[80]

A study by Kieran *et al* published in 2015, estimated that the mean annual direct medical cost of untreated HCV infection in Ireland ranged from €398 in patients with mild liver disease to €21,992 for a patient with HCC. Patients in the first year post-transplantation accrued the most costs (€137,176) [81]. This study demonstrated that the direct medical costs of untreated HCV in Ireland are substantial and these costs increase exponentially with the progression of liver disease. A second study by Kieran *et al*, also published in 2015, that aimed to establish the budget impact of HCV treatment in Ireland from 2001-2012, identified that during this period the number of patients treated per annum peaked in 2009 [82]. Overall, during this period, 2,320 individuals received treatment with PR, the standard of care at the time. The budget impact was significant with €27 million spent on providing drug treatment for HCV from 2001-2012. However, the number of patients treated during this period was relatively

modest. This is likely due to the fact that treatment with PR treatment regimen was resource intensive and patients required a substantial amount of support and monitoring, thus, limiting the number of patients that could receive treatment at any one time. Given that the all-oral DAA regimens are shorter in duration and are associated with a reduction in side effects, budget impact assessments must anticipate an increase in treatment capacity, and subsequent increase in the cost of providing drug treatment, over the coming years.

2.8 Treatment of Chronic Hepatitis C

The goal of therapy for chronic HCV infection is eradication of the virus. The end point of successful therapy is SVR24, defined as undetectable HCV RNA in serum 24 weeks after treatment has been completed [25]. A recent study demonstrated that undetectable HCV-RNA at 12 weeks after completion of treatment (SVR12) correlates closely with SVR24 and thus, SVR12 can be effectively used to determine “cure” rates in trials and clinical practice and is now accepted as a primary study endpoint by most regulatory bodies [83, 84]. With an array of treatment currently available, it is important that treatment decisions are individualised. Decisions may be based on the genotype, stage of liver fibrosis, previous treatment experience, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient’s readiness for treatment [1, 49]. Since first identified in 1989, significant advances have been made in the treatment of HCV infection (Figure 4).

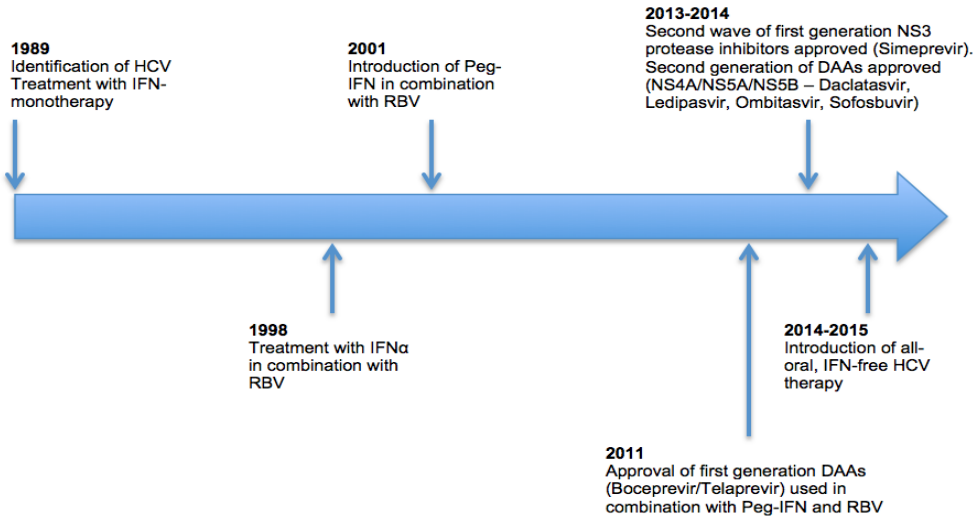


Figure 4: HCV Treatment Timeline
Peg-IFN = pegylated-interferon, RBV = ribavirin

2.8.1 Treatment Paradigm 1989-2001

In the first two decades after the discovery of the virus, the evolution of treatment for HCV was slow, mainly due to the poor understanding of the viral life cycle. Historically, IFN-α-based monotherapy was the standard antiviral regimen for the initial management of HCV. However, SVR rates were poor ranging from 5%-20% [85-87].

Ribavirin (RBV) is a nucleoside analogue with activity against a number of viruses. The mechanism of action is complex and not completely understood but possibilities include direct inhibition of HCV and modulation of innate and adaptive antiviral immune responses including an augmented induction of IFN-stimulated genes in response to IFN-α [86]. While RBV alone had little effect on HCV-RNA levels, the addition of RBV to IFN-α improved SVR rates by more than two-fold (~38%) [87]. Therefore, in 1998, IFN-α in combination with RBV was approved for the treatment of HCV infection.

2.8.2 Treatment Paradigm 2001-2011

The third significant breakthrough in the treatment of HCV was the approval of pegylated-interferon-α (Peg-IFN) in 2001 [86]. The pegylation of IFN-α resulted in profound pharmacokinetic changes characterised by higher and longer-lasting serum concentrations, thus, requiring less frequent dosing. From 2001 to 2011, dual therapy with PR became the standard of care for treating HCV infection.

While there were significant improvements in the SVR rates, these differed substantially between patient populations [88]. One important predictor of SVR is genotype. PR for 48 weeks resulted in SVR rates of approximately 40%-50% in HCV GT1-infected individuals but 24 weeks of PR therapy usually resulted in a SVR in 70%-90% of GT3 and GT2-infected individuals, respectively [86, 89]. Host determinants such as race, presence of metabolic syndrome, or presence of advanced liver fibrosis are other important predictors of treatment response.

Treatment with PR was associated with significant side effects and were regarded as a major limitation to therapy [90]. Fatigue, influenza-type symptoms, psychiatric morbidity and haematological abnormalities were commonly associated with Peg-IFN. The psychiatric symptoms mandated careful patient selection and monitoring, and in some cases, precluded some patients from accessing therapy. RBV caused anaemia and was also associated with rash and pruritus. These adverse effects (AEs), in addition to the long duration of treatment, often affected treatment uptake and patient adherence, which impacted the efficacy of treatment [91].

2.8.2.1 IL28B Haplotype

In 2009, four independent groups, using genome wide association studies, identified single nucleotide polymorphisms (SNPs) near the interleukin-28B (IL28B) region which were strongly associated with response to PR [92, 93]. The SNP has three genotypes: CC, CT and TT [94]. Patients with a favourable IL28B CC genotype are more likely to have a SVR with PR treatment, whereas patients who have the TT genotype are more likely to be non-responders. These genetic variants also affect viral kinetics on-therapy and during spontaneous viral clearance [95].

2.8.3 Treatment Paradigm 2012-Present

Recent years have seen a significant improvement in the treatment of HCV infection, with the advent of DAA therapy and a move towards potent IFN-free regimens, with SVR rates above 90% [96]. An improved understanding of the HCV life cycle and replication has allowed for the development of a plethora of new therapeutic agents that target enzyme activity directly [88, 90].

2.8.3.1 Interferon-based Regimens

The NS3/4A inhibitors target the serine protease NS3/4A which cleaves the HCV polyprotein at four sites [88]. First generation protease inhibitors, telaprevir (TPV) and boceprevir (BOC), were the first DAAs to be licensed for HCV GT1-infected individuals in 2011. Both agents were used in triple therapy regimens in combination with a PR backbone for 24 or 48 weeks (BOC/PR and TPV/PR) [88]. The treatment protocols for these regimens varied depending on whether the patient had previously received treatment for HCV, whether or not they are cirrhotic, in addition to their HCV-RNA response during therapy (Figure 5 and Figure 6).

RCTs for these regimens reported a significant improvement in efficacy in both treatment naïve and treatment-experienced GT1 patients compared to dual therapy (PR) alone (67%-75% vs. 40%-44% in treatment naïve patients, 31%-86% vs. 5%-29% in treatment-experienced patients) [97-105]. Despite improved SVRs rates, these regimens were associated with additional AEs. Both regimens had significantly increased rates of anaemia compared with PR alone. Up to 50% of patients in the BOC/PR RCTs reported anaemia while TPV/PR therapy resulted in severe rash in addition to anaemia. As a result of a variety of host, viral and treatment-related factors, therapeutic regimens incorporating first-generation protease inhibitors were complex [106]. A combination of a challenging side effect profile, drug-drug interactions, low barriers to resistance, lack of pangenotypic activity and a requirement for intensive on-treatment monitoring leading to a reduction in the capacity to treat patients has limited the effectiveness of this drug class [107]. Careful patient selection and monitoring was essential to ensure positive clinical outcomes and minimisation of patient morbidity [108].

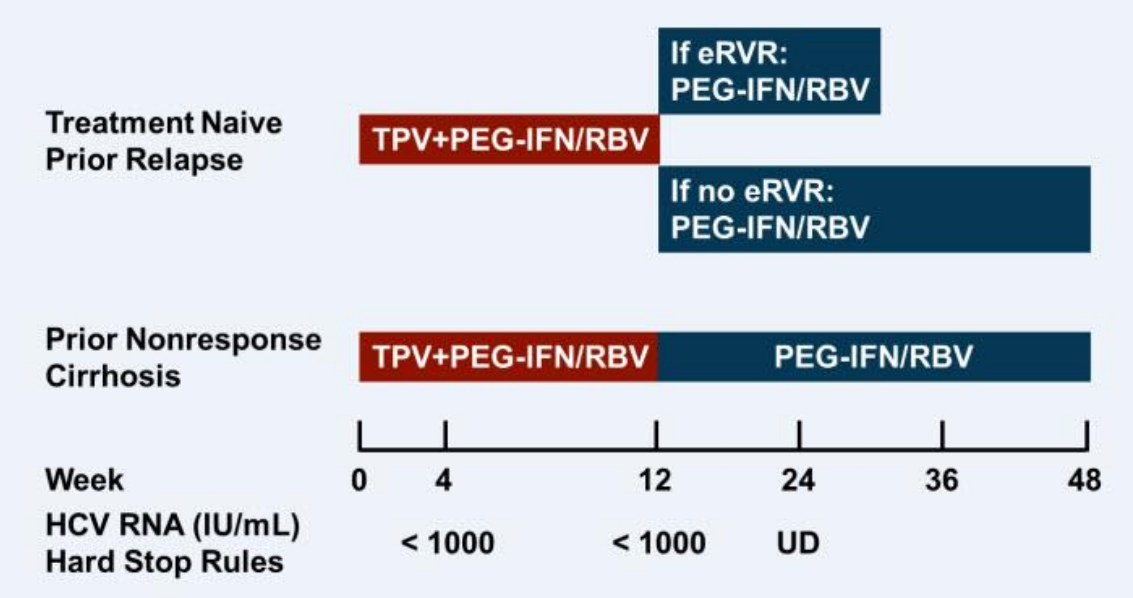


Figure 5: Telaprevir triple therapy treatment paradigm
Sourced from Schiffman M.L [109]
TPV = Telaprevir, PEG-IFN = pegylated-interferon, RBV = ribavirin, eRVR = early rapid virological response

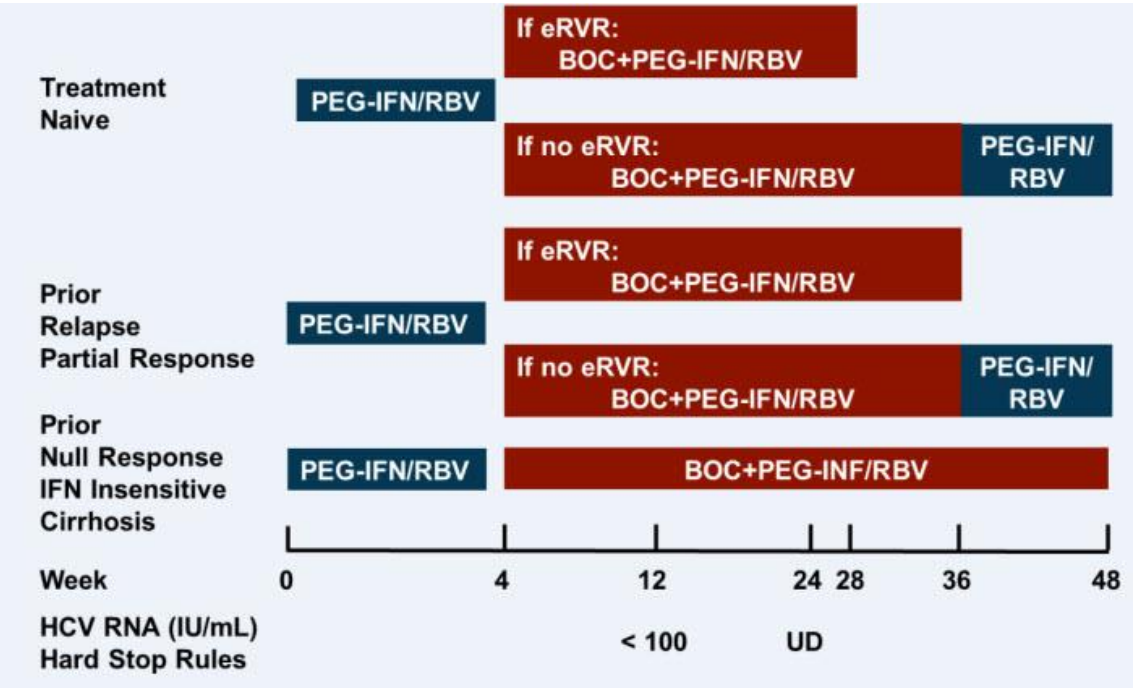


Figure 6: Boceprevir triple therapy treatment paradigm
Sourced from Schiffman M.L [109]
BOC = Boceprevir, PEG-IFN = pegylated-interferon, RBV = ribavirin, eRVR = early rapid virological response

In 2013, simeprevir (SMV), a second wave protease inhibitor that was licensed for use in GT1 and GT4 HCV infection in combination with a PR backbone (SMV/PR), was approved for use in Ireland. Treatment duration is between 24 and 48 weeks. RCTs reported SVR rates of approximately 80% in treatment naïve patients and 77%-89% in treatment-experienced patients [110-113]. The overall safety profile of SMV/PR was better than for TPV/PR and BOC/PR triple therapy, with only a small proportion of patients reporting rash, pruritus, photosensitivity and hyperbilirubinaemia [114].

Daclatasvir (DCV), an NS5A inhibitor, was evaluated in combination with a PR backbone (DCV/PR). In GT1 individuals, the treatment duration was 24 to 48 weeks and SVR rates ranged between 57%-87%, with lowest rates observed in GT1a individuals. In GT2 and GT3-infected patients, 12-24 weeks of treatment was required. Efficacy rates in GT2 patients ranged from 83%-88% and were approximately 70% in GT3-infected individuals [115]. While SVR rates in some patient populations were

promising, NS5A inhibitors are predominantly used as components of IFN-free regimens, and not in a triple therapy regimen with a PR backbone.

Sofosbuvir (SOF), an NS5B inhibitor, in combination with PR, was licensed for treatment in all genotypes (SOF/PR). Treatment duration was between 12-24 weeks. The RCTs reported SVR rates of 91% in GT1-infected patients, 83%-96% in GT2/3-infected patients and 87%-90% in GT4/5/6-infected patients [116-118]. The site of action of the DAA agents is illustrated in Figure 7 [88].

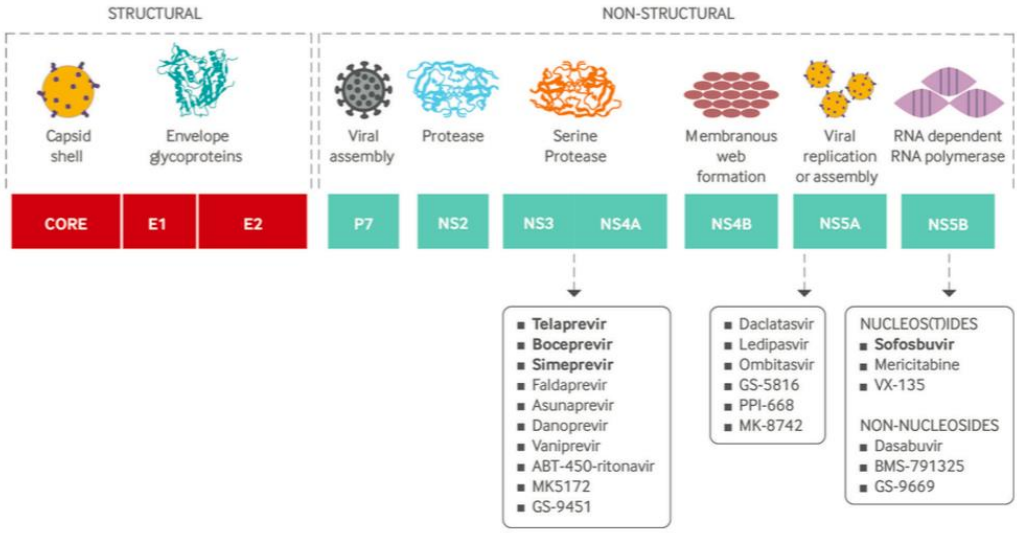


Figure 7: Sites of action of the direct-acting antiviral agents

2.8.3.2 Interferon-free Regimens

With an urgent need for more effective antiviral therapy for difficult to treat populations with IFN intolerance, availability and accessibility of all-oral, IFN-free regimens was the next step forward [114]. These advances in therapy resulted to improved efficacy with higher SVR rates [119]. Other promising characteristics of these new regimens included improved tolerability, a reduced pill burden and a reduced potential for drug-drug interaction while also shortening the duration of treatment [120].

Given its pangenotypic activity, there are a number of sofosbuvir-combination regimens that have demonstrated improved efficacy in a multitude of patient populations. Sofosbuvir with or without ribavirin (SOF±RBV) has been approved for use in all six genotypes. SVR rates range from 67%-93% with the lowest efficacy rates observed in GT1-infected individuals and GT2/3 previous non-responders [88, 121]. Treatment duration is for 12 weeks with the exception of GT1 patients, where 24 weeks is recommended. Sofosbuvir combined with simeprevir with or without RBV (SOF/SMV±RBV) is an option for GT1 and GT4 individuals. SVR rates in the GT1 population were 79%-96% after 12 weeks of therapy. While this combination has not been studied in RCTs, the European Association for the Study of Liver Disease (EASL) recommended its use in the GT4 population [122, 123]. Sofosbuvir showed promise when combined with NS5A inhibitors, ledipasvir (SOF/LDV±RBV) and daclatasvir (SOF/DCV±RBV), with or without ribavirin. RCTs studying SOF/DCV±RBV for 24 weeks reported SVR rates of 98% in a GT1 population and 93% in a GT2/3 population [124]. When combined with ledipasvir (SOF/LDV±RBV), SVR rates in GT1 patients ranged from 94%-99% following 12-24 weeks of therapy [125-127].

The final licensed regimen is a combination of the NS3/4A inhibitor paritaprevir, co-formulated with low dose ritonavir and the NS5A inhibitor ombitasvir, which is administered in combination with dasabuvir, an NS5B nucleoside inhibitor, with or without ribavirin (3D±RBV). This regimen is licensed for use in GT1-infected individuals with treatment duration ranging from 12-24 weeks. RCTs have reported SVR rates between 90%-99% [88, 114, 128-130]. Table 2 presents the range of SVR rates reported in the pivotal clinical trials for each DAA regimen.

Table 2: SVR rates for DAA regimens reported in randomised controlled trials

Treatment Regimen	Genotype	SVR Rate (%)
TPV/PR	1	31-86
BOC/PR	1	40-68
SMV/PR	1/4	77-89
DCV/PR	1	57-87
	2	83-88
	3	70
SOF/PR	1	91
	2/3	83-96
	4/5/6	87-90
SOF+RBV	1/2/3	67-93
SOF/SMV±RBV	1	76-96
SOF/LDV±RBV	1	94-99
SOF/DCV±RBV	1	98
	2/3	93
3D±RBV	1	90-99

Given the myriad of available treatment regimens, in 2015, EASL published updated recommendations on the treatment of HCV infection [122]. These recommendations were intended to assist physicians and other healthcare providers in the clinical decision-making process by describing the optimal treatment regimens for the management of individuals, with or without cirrhosis, infected with HCV. For all regimens, the recommended duration of treatment and reported SVR rates often differed depending on whether the patient has cirrhosis or not (Figure 8 and Figure 9).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Figure 8: Treatment recommendations for HCV-infected individuals without cirrhosis
Including both treatment naive and treatment experienced (PR failure) individuals
Sourced from EASL Recommendations 2015 [122]

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Figure 9: Treatment recommendations for HCV-infected individuals with compensated cirrhosis
Including both treatment naive and treatment experienced (PR failure) individuals
Sourced from EASL Recommendations 2015 [122]

Since the publication of the above recommendations in 2015, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) have published updated HCV guidelines which include recommendations for the use of two additional all-oral DAA regimens [131]. Elbasvir and grazoprevir, a fixed-dose combination, was approved in early 2016. Elbasvir is a NS5A inhibitor while grazoprevir is a NS3/4A inhibitor. The combination is licensed for use in

GT1 and GT4 HCV infection. High efficacy rates of 95% were reported in clinical trials, even in difficult-to-treat patients such as those with cirrhosis, HIV co-infected, those who had failed previous therapy and dialysis-dependent patients [132-136].

A second fixed dose combination, sofosbuvir and velpatasvir was approved by the European Medicines Agency (EMA) in July 2016. Velpatasvir is a novel NS5A inhibitor. It is the first once-daily single tablet regimen with pangenotypic activity licensed for use in patients with GT1-6 without cirrhosis and with compensated cirrhosis. The addition of ribavirin should be considered for GT3 infected patients with compensated cirrhosis and is recommended in patients with decompensated cirrhosis. Efficacy rates of 97%-100% were reported in clinical trials [137-139]. Neither of these treatment combinations are currently approved for use in Ireland.

2.9 Cost of Hepatitis C Treatment

The cost of treating HCV infection is substantial and continues to rise. PR was the standard of care for a decade. During this period, Stahmeyer *et al* and Solomon *et al* estimated that the direct medical costs of treatment were between €19,000 and €25,500 ($28,500) [140, 141]. Despite enhanced SVR rates, which correlate to cure, protease inhibitor regimens were associated with significant additional costs [142].

In Ireland, the drug acquisition costs for TPV/PR were between €36,000 and €48,000 depending on the treatment duration while the costs for BOC/PR were between €31,000 and €57,000. For both TPV/PR and BOC/PR, budget impact analysis indicated an expenditure of approximately €1.1 million, respectively, in year one. Over a five year period, the estimated expenditure was €5.2 million and €6.5 million, for TPV/PR and BOC/PR, respectively [143, 144].

While the new second generation, IFN-free combination DAA agents are considered to be more efficacious with SVR rates >90%, they are also accompanied by a significant increase in the cost of the treatment regimen [145]. The drug acquisition costs of these agents are considerable. A 12-week supply of SOF/LDV is approximately €46,000, increasing to €96,000 should 24-weeks of treatment be required [146]. The budget impact in Ireland is difficult to predict. While it is estimated that between 6,000-8,000 patients with HCV infection are engaged in care and remain untreated, the number of patients that will be treated over the next 5 years depends on capacity, budget availability and the outcomes from increased screening programmes. In an era of ever-increasing drug costs within a fixed budget, health technology assessments (HTA) are requiring input data from various sources, including robust real world data, to estimate the cost and consequences of HCV treatment and enhance reimbursement decisions [8].

In recent years, several new DAAs have become available to treat HCV infection and have undergone economic assessment in Ireland, as in other healthcare jurisdictions. For these assessments, input data from various sources were used to estimate the costs and consequences of HCV treatment, as data from Ireland was not available. Like other healthcare systems worldwide, there are significant concerns about the potential budget impact of these agents, given the burden of HCV disease and the high acquisition cost of the new therapies [82].

2.10 Health Economic Assessment in Ireland

Health economic assessment has been defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" [147]. It involves the identification, measurement, valuation and comparison of costs and consequences associated with a particular health investment decision where there are competing options. There are different types of health economic analysis undertaken,

which are differentiated largely by the differences in the way they value outcomes [147, 148].

The preferred method of health economic assessment in Ireland is cost-utility analysis [149]. Cost utility analysis typically values the consequences 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 (QALY), which allows comparison of outcomes across different technologies.

When it comes to modelling outcomes in cost-utility analysis, decision trees and Markov models are two types of economic models. The decision tree is the simplest form where outcomes of treatments are compared against each other over a single defined period of time and the costs and consequences of individual strategies are calculated for the intervention. For modelling a chronic disease with multiple consequences over long periods, a Markov model is more appropriate. This model is run in cycles with patients transitioning from mutually exclusive health state to health state in accordance with typical disease progression [148, 149]. 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 evidence base informing economic evaluations is rarely derived from a single source [150]. More commonly, the evidence base informing the model parameters is represented by many data sources including individual patient-level data, RCTs, observational studies, expert opinion and secondary data analyses [151]. For economic models to be useful decision aids, it is important the inputs are appropriately selected

to ensure model validity. Real world data from well-designed studies can be valuable for informatively evaluating the cost-effectiveness of competing treatments.

Results of economic analyses are generally plotted using the cost-effectiveness plane. This compares incremental costs on the Y-axis to incremental effectiveness on the X-axis (Figure 10).

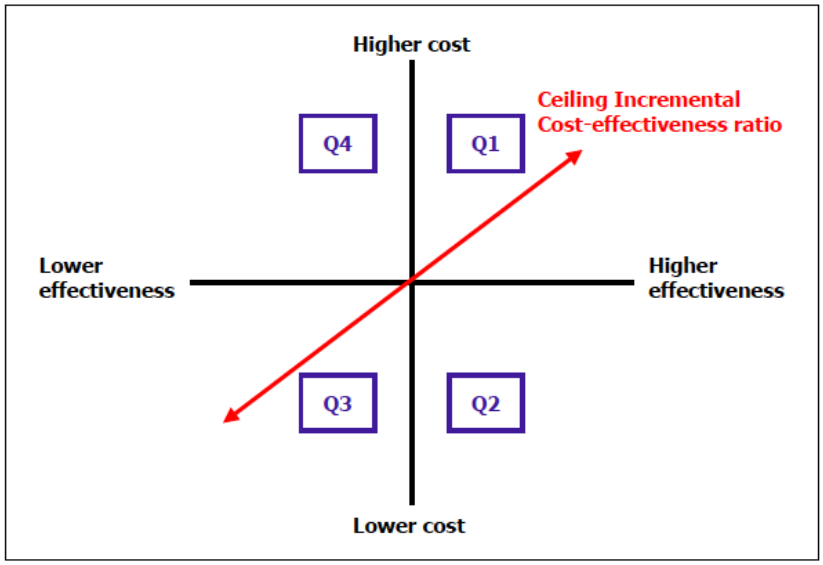


Figure 10: Cost-effectiveness plane
Sourced from HIQA Guidelines for Economic Evaluations [149]

The quadrants are labelled 1-4. Most new technologies fall into Q1 i.e. they usually have an effectiveness gain with a corresponding increase in price. Technologies that are plotted in Q4 cost more and are less effective then the current standard of care and would generally be excluded from consideration. Occasionally new technologies cost less and are more effective (Q2) or they are less effective but cost less (Q3). Technologies in Q2 are always considered cost-effective and those in Q3 may be worth considering in the setting of budget constraints [147, 149, 152].

The results of a cost-utility analysis are presented as an incremental cost-effectiveness ratio (ICER). This describes how much additional benefit is achieved for the additional cost incurred. The ICER for two technologies A and B is calculated as follows:

ICER = (Cost of A – Cost of B)/(Effects of A – Effects of B)

The cost-effectiveness plane can also be used to display the willingness to pay (WTP) threshold. This is the threshold ICER below which technology would always be reimbursed [147, 153]. Since 2012 in Ireland, this has been set at an ICER of €45,000/QALY. However, not all technologies that have ICERs below this threshold 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 they address [154-156].

2.11 Treatment in the Irish Setting

Following HTAs conducted by the National Centre for Pharmacoeconomics (NCPE), TPV/PR and BOC/PR regimens were approved for use in Ireland in 2012. Given the significant side effect profile of these treatment combinations, suitable patients were carefully selected for treatment by physicians. As a result of the findings from a study by Hezode *et al,* many patients with advanced cirrhosis were withheld from treatment [157]. This study reported that, in cirrhotic patients exposed to protease inhibitor triple therapy regimens (e.g. TPV/PR or BOC/PR), albumin levels <35 g/L and platelet count ≤100,000m^3 were independent predictors of death or severe complications.

In late 2014, the Irish healthcare provider granted early access to the IFN-free regimens before the Health Service Executive (HSE), the payer, in Ireland, made the final recommendations around cost-effectiveness and reimbursement. Given that the cost of these drugs created a significant burden on the healthcare system, a phased

treatment strategy was required to address the issue of affordability. The universal approach was aimed at prioritisation based on clinical need. The proposed clinical criteria were to focus on those patients with greatest clinical need and particularly those patients with a risk of death or irreversible damage within the next 12 months. The clinical criteria were based on international evidence and expertise [76, 158].

In December 2014, the first IFN-free regimen, SOF/LDV±RBV (for 12 weeks) became available in Ireland following authorisation of an early access program (EAP) by the HSE. Patients were eligible for treatment if they met at least one of the following criteria:

- Evidence of present or previous decompensated cirrhosis defined as an episode of ascites, variceal bleeding, spontaneous bacterial peritonitis or hepatic encephalopathy.
- Child Turcotte Pugh (CTP) Score ≥ 7 (CTP B or CTP C)

By April 2015, three IFN-free regimens SOF/LDV±RBV, 3D±RBV and SOF/DCV±RBV were available in Ireland. At this stage, in addition to the above listed criteria, patients that demonstrated evidence of compensated cirrhosis (Child Pugh Score < 7 (CTP A)) were also eligible for treatment.

By June 2016, availability of treatment had been extended to patients who contracted HCV directly or indirectly through the administration, within the State, of the anti-D immune globulin or another blood product or blood transfusion. Additionally, this phase also included patients who have undergone orthotopic liver transplant. Patients were not required to demonstrate evidence of cirrhosis.

This phased treatment program is intended to provide drug treatment to those with greatest clinical need as a priority, treating as many patients as possible within a fixed budget. It is proposed that this approach will impact on the prevalence of HCV over a decade and will ensure more HCV-infected patients will be treated sooner.

Chapter 3

Chapter 3 Observational Research

Studies of observational design are used to measure the effectiveness of an intervention in non-experimental, real world scenarios at the population level [159]. Although not perceived as the gold standard, observational studies can play an integral role in evaluating the treatment effect. The evidence from these studies can complement clinical trials. If evidence generated by clinical trials and observational studies is consistent, the additional real world evidence would be expected to reduce uncertainty surrounding relative treatment effects and aid decision-making [160]. Despite their methodological challenges, observational studies can play an important role in strengthening the existing evidence base [161].

3.1 Randomised Controlled Trials

The RCT is a trial in which subjects are randomly assigned to one of two groups: one (the experimental group) receive the intervention that is being tested, and the other (the comparison or control group), receive an alternative (conventional/placebo) treatment [162]. RCTs have been considered the gold standard in the hierarchy of research designs and indispensible tools for evaluating the efficacy and safety of treatment interventions before their launch [11-13]. However, their results have limited applicability to patients in clinical settings [163, 164]. The great strength of RCTs is that the allocation of treatment is random so that the groups being compared are similar in baseline factors. This ensures a secure method of attributing causality in observed associations between treatments and beneficial outcomes [11, 12, 165]. Clinical trials tend to use precise clinical endpoints and employ strict inclusion and exclusion criteria, in order to eliminate factors that might confound or obscure treatment effects. Additional strengths and limitations of RCTs are outlined in Table 3.

Table 3: Strengths and limitations of randomised controlled trials [11-13, 163, 164]

Strengths	Limitations
Well-defined study population	Excludes many patients requiring clinical treatment
Design maximises internal validity	Outcomes are difficult to extrapolate to a more general patient population
Tightly controlled treatment conditions	Short duration and small sample sizes limit ability to identify rare or long-term adverse events
Compliance maximised through strict protocols	

Validity refers to a lack of systematic error. Internal validity implies that the differences observed between groups of patients allocated to different interventions may, apart from random error, be attributed to the treatment under investigation. In contrast, external validity, or generalisability, is the extent to which the results of a study provide a correct basis for generalisations to other circumstances [166]. Internal validity is a prerequisite for external validity [167]. That is, the study must demonstrate that the "exposure" in the study is the cause of variation in the outcome before one can generalise that the exposure more universally causes the outcome. Introduction of bias undermines the internal validity of research [168].

3.2 Observational Studies

Observational research involves the direct observation of individuals in their natural setting [167]. It is becoming increasingly recognised as an important component of the evidence pyramid [14]. The use of observational research is vital in building the evidence base, identifying the best practices and understanding disparities in access to, and delivery of, healthcare [167]. They should not be used to replace RCTs but can be very useful in complementing the results of such trials. Observational studies use real world populations comprising even the most complex patients, delivering results to clinicians, decision-makers and patients, about which interventions are most effective in specific subpopulations [169]. Observational studies have provided information about important clinical questions that would never be addressed by a RCT and they identify gaps in care after RCTs have been published [170]. Observational data can provide valuable

information regarding the effectiveness and appropriate use of agents in the real world, outside of clinical trials [15]. Studies can demonstrate whether clinical trial results hold true in clinical practice. Data can also extend support for the use of a treatment in a patient population not included in the original clinical trial [11]. Properly conducted observational studies, like RCTs, are important for modifying clinical practice by reducing uncertainty [171]. Furthermore, they can identify findings that warrant further investigation in controlled trials. Observational studies are an underappreciated but valuable source of data, and these data are essential for making sound decisions regarding coverage and reimbursement [15].

Observational studies should collect data rigorously and systematically [172]. They can often incorporate a large and diverse patient population, and be completed at a lower cost than RCTs [11, 173-175]. Additionally, this type of study does not involve any investigator intervention and is not considered to be obtrusive to the population under investigation [176]. Further advantages and limitations of observational studies are presented in Table 4.

Table 4: Strengths and limitations of observational study methodology *[11-13, 164]*

Strength	Limitations
Real world, clinical populations	Non-randomised nature: Selection bias, leading to problems in determining causality
Large diversity of patients and practices	Available data limited to variables in the data source
Longer observation periods	Possible under-reporting or incorrect coding
Can capture data on persistence and compliance with treatment	Potential for confounding variables (i.e. inability to control for all other factors that may vary between two groups)
Identification of infrequent, long-term adverse events	
Lower costs than randomised controlled trials	
Numerous outcomes can be studied	
Suited to long-term follow-up, sometimes over decades or more	
Less affected by ethical considerations than RCTs if only using data that have already been collected in routine clinical practice	

The major challenge associated with observational research is validity, both internal and external. Internal validity remains the most contentious issue and the major weakness of observational studies, which refers to the possibility that selection bias, information bias or confounding bias will influence the results of the study [172, 177, 178].

3.2.1 Bias in Observational Research

Selection bias, information bias and confounding bias are present to some degree in all observational research [161, 162, 178]. The challenge for those interpreting study results is to identify these sources of potential bias and determine how they may have affected results.

3.2.1.1 Selection Bias

Selection bias occurs when the selected study participants are systematically different in characteristics from eligible participants who are not selected for the study. Additionally, when the exposed and unexposed groups are different in important outcome predictors, the results might be biased [168, 179-182]. It can occur as a natural consequence of the study design or during the implementation of a research protocol [183]. Selection bias may lead to confounding bias.

3.2.1.2 Confounding Bias

Confounding bias can be defined as a systematic error that occurs as a result of the influence of one or more risk factors for an outcome of interest, leading to a distortion of the true measure of association [184]. It occurs when the distribution of risk factors that leads to an over-estimation or under-estimation of the true effect is unbalanced across comparison groups. The association of these risk factors with both the intervention and the outcome can lead to type I errors, in which the outcome of the intervention are falsely attributed to the intervention rather than the confounding variable. Alternatively,

confounding can lead to type II errors, in which the study incorrectly concludes that there is no treatment effect [179]. A factor can be a confounder (*L, measured; U,* unmeasured) only if that factor is associated with drug treatment (*T*) and is also an independent risk factor for the study outcome (*Y*) (Figure 11).

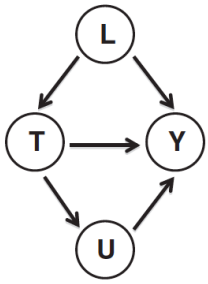


Figure 11: Causal diagram demonstrating the mechanics of confounding

Y, L, U and T, respectively denote the outcome, a set of measured confounders, a set of unmeasured confounders and the treatment.
Sourced from Quartey et al [184]

Confounding is particularly problematic in observational research because the investigator does not actively take part in the allocation of exposure (e.g. through randomisation) but simply observes how they were distributed. While RCTs allow for the balancing of confounders during the design stage, observational studies require adjustment for confounders at the analysis stage [185]. A number of approaches have been developed to reduce or eliminate the issue of confounding.

3.2.1.3 Information Bias

Information bias refers to systematic errors in the measurement of the exposure or outcome [182]. It results from wrong or inexact recording of individual factors, either risk factors or diseases being studied [186]. Detection bias, observer/interviewer bias, recall bias and reporting bias are the most common types of information bias. Detection bias refers to systematic differences between study groups in how outcomes are determined. Observer/interviewer bias can occur if those responsible for assessing or recording outcomes know which patients are allocated to each of the study groups,

and, consciously or unconsciously, record the outcomes for the patients receiving the intervention under investigation in a more favourable way than those receiving the comparator. Recall bias is a systematic error caused by differences in the accuracy or completeness of recollections retrieved from study participants regarding events or past experiences and reporting bias refers to participants providing responses in the direction they perceive are of interest [186-188]. Blinding and concealment are methods used in RCTs to eliminate/reduce these biases.

The potential for bias in observational research is higher than in RCTs. Observational research does not have the benefit of randomisation to allocate, by chance, the risk factors for an outcome of interest. A number of design and analysis features will be discussed later in this chapter that can address these concerns although they cannot completely eliminate them [173, 189].

3.2.2 Types of Observational Research Methods

There are a number of different methods for undertaking observational research. Studies can be classified as cohort, case-control or cross-sectional [190]. Epidemiological studies analyse patterns, causes and effects of health and disease conditions in defined populations whereas pharmacoepidemiology is the study of the uses and effects of drugs in well defined populations.

3.2.2.1 Cohort Studies

The cohort study is the closest in design to a clinical trial [191]. They are extremely relevant for scientific discovery, informing the design of RCTs and assessing effectiveness in clinical practice. Cohort studies are considered the most reliable form of observational study and are important when the use of RCTs may be unethical [191]. In

a prospective cohort study, subjects who do not have the outcome of interest are recruited to participate. The subjects are observed over a period of time to determine whether they develop the outcome of interest [177]. In a retrospective study, data that has already been collected for other purposes is used. Cohort studies are the best method of ascertaining both the incidence and natural history of disease [192]. Additionally, a single study can be used to examine various outcome variables and is also useful, but not optimum, in the study of rare exposures [190]. Pharmacoepidemiological studies, another form of cohort study, are concerned with estimating the efficacy, effectiveness and safety of therapeutic interventions [193]. The main disadvantages of cohort studies are the requirement for large sample sizes and the potentially long follow-up period, leading to increased costs. Loss to follow-up can also be problematic, particularly in those with long follow-up periods. A patient not experiencing the outcome may be more likely to be lost to follow-up than a patient experiencing the outcome, which can bias the study results [167, 192]. As with all observational studies, cohort studies are subject to various types of bias.

3.2.2.2 Cross-Sectional Studies

A cross-sectional study is an observational study in which the exposure and the outcome are determined at the same time point for each study participant and are primarily used to study prevalence [167]. Prevalence describes the number of cases in a population at a given time point [177]. Researchers aim to obtain a representative sample by taking a cross-section of the population [194]. All measurements for a single member are obtained at a single point in time. These studies are also used to infer causation. They are useful for examining the burden of disease and for health service planning [167]. They are generally quick, easy and cheap to perform and there is no loss to follow up, since participants are interviewed only once. However, this type of study is prone to a number of types of biases. Selection bias may occur if the study participants are

systemically different in their characteristics compared with eligible participants who were not selected for the study [167, 195]. A common type of selection bias is non-response bias, where participants who consent to take part in the study differ from those who do not, resulting in a sample that is not representative of the population. Since information on exposure and outcome are recorded simultaneously, prior knowledge of the condition might influence ascertainment of the exposure or the outcome, therefore, both recall and detection bias are likely [196]. Finally, confounding is also an important issue. Confounding occurs when the exposed and unexposed groups are different in some way that is also related to the outcome [185].

3.2.2.3 Case-Control Studies

Case-control studies are usually retrospective. A group of subjects with the outcome of interest are identified and matched to a control group without the outcome of interest [177]. The research retrospectively determines which subjects were exposed to the agent or treatment, or determines the prevalence of a variable in each of the study groups [177]. Case-control studies are well suited to investigate rare outcomes or outcomes with a long latency period because subjects are selected from the outset by their outcome status. They are relatively easy and inexpensive to conduct compared with cohort studies and loss to follow-up is not an issue [190, 191]. The familiar issues of bias and confounding are common problems with case-control studies. While suitable for the study of rare diseases, they are not suitable for the study of rare exposures due to difficulties recruiting the required sample size [197].

3.2.3 Methods for Dealing with the Limitations of Observational Studies

There are many design and analysis features that can address the limitations of observational research although they cannot completely eliminate them [173]. A number of approaches have been developed to reduce the issue of confounding. These

include, but are not limited to, method matching (in case control studies), stratification of known confounding factors, direct adjustment when the relationship between the response, exposure and confounders is well established and multivariable regression analysis. More advanced techniques include the use of propensity scoring, instrumental variable methods, sample selection models and marginal structural models [184, 185].

3.2.3.1 Regression Analysis

Regression analysis is one of the most commonly used analytical techniques to control for confounding. It is based on modelling the mathematical relationships between two or more variables that give an approximate description of the observed data. After initially examining the relationship between the exposure of interest and the outcome (giving a “crude” or “unadjusted” result), variables that are known confounders are then added to the model to provide an effect that is “adjusted” for these known confounders [185]. Multiple logistic regression is commonly used in observational research to assess the relationship between certain exposures or treatments and a binary outcome while controlling for confounding and effect modifiers [198]. This analysis allows for the association between dependent and independent variables to be estimated while controlling for the influence of other independent variables [199]. Multivariable regression allows for models that include many confounders. The problem with such a method is that many factors may lead to the loss of power. Moreover, if the confounder is unknown or unmeasured, then this method is useless.

3.2.3.2 Propensity Score Analysis

Conventional multivariable analysis may not always be the ideal method for estimating treatment effects in observational studies. When there are large differences in the distribution of covariates between treatment groups, adjusting for these differences

with conventional multivariable techniques may not adequately balance the groups, and the remaining bias may limit valid causal inferences [198]. Propensity score (PS) analysis, which will be applied in this thesis, is another approach that is used with increasing frequency to account for confounding [200, 201]. It is a type of statistical method developed for estimating treatment effects with non-experimental or observational data [202]. While it is by no means conceived as the best alternative to randomised experiments, there is a consensus among prominent researchers that the PS approach has reached a mature level and that it is a tool that has much to offer researchers. It may adjust covariates between the two groups and reduce bias better than conventional multivariable modelling.

This method involves the generation of a score that summarises the confounding by multiple variables. The PS has been described as a conditional probability, between 0 and 1, that a subject will be treated based on an observed group of covariates. The collection of confounding covariates is collapsed into one score or propensity to have received one treatment over the other, based on a larger collection of covariates available in the dataset [198]. The PS is known as a balancing score: conditional on the PS, the distribution of measured baseline covariates is similar between treated and untreated subjects. Thus, in a set of subjects all of whom have the same propensity score, the distribution of observed baseline covariates will be the same between the treated and untreated subjects [203]. When patients in one treatment group differ systematically from those in other treatment groups, minimising the bias through the use of a PS can make direct comparisons more meaningful [198, 199]. In practice, the PS is often estimated using a logistic regression model, in which treatment status (i.e. untreated or treated) is regressed on observed baseline characteristics. The estimated PS is the predicted probability of treatment derived from the fitted regression model. Four methods of using the PS have been described in the literature: propensity score

matching, stratification (also known as subclassfication), inverse probability of treatment weighting (IPTW) and covariate adjustment using the PS [202-204].

PS matching entails forming matched sets of treated and untreated subjects with similar values of the propensity score. Although there are different approaches to matching, the most common approach in the medical literature is nearest neighbour matching without replacement within a specified caliper limit of the PS, and we will use this methodology in this thesis [201, 204-206]. Using this approach, pairs of treated and untreated subjects are formed such that the PS of the matched subjects lies within a specified distance of one another (the caliper width). Naïve matching is also possible, where no limit is placed on the caliper width. All treated subjects are matched to untreated subjects until every subject has been matched. This method assumes that within the matched sample, treated and untreated subjects have similar distributions of baseline covariates.

Stratification on the PS involves comparing outcomes between treated and untreated subjects within strata [204, 205]. The most common approach is to use five approximately equal sized strata defined by the quintiles of the PS. Rosenbaum and Ruben demonstrated that stratifying on the quintiles of the estimated PS eliminates approximately 90% of the bias due to measured confounders [207]. Treated and untreated subjects are compared within each stratum. This method assumes that within each stratum, treated and untreated subjects have a similar distribution of baseline covariates [204, 205].

With inverse probability of treatment weighting, weights, which are based on the propensity score, are used to ensure that the distribution of measured baseline

covariates is the same in treated and untreated subjects. The distribution of covariates is changed in both the treated and untreated subjects so that they are the same as the distribution in the entire sample [203].

The final method of propensity score analysis is covariate adjustment. In this method, the outcome variable, which for this research would be 'SVR achieved' or 'SVR not achieved', is regressed on a dummy variable denoting treatment status, with or without other covariates and the estimated propensity score. When the outcome is binary, a logistic regression model is used. The effect of treatment is determined using the estimated regression coefficient from the fitted regression model [203, 204].

Each method of propensity score analysis has advantages and disadvantages [208]. PSM is the superior method for reducing bias. Additionally, it is a transparent and easy-to-follow method and, similar to a RCT, the outcomes between treated and controlled participants in PSM can be directly compared. PSM is also considered to be the most robust method to misspecification of the propensity score model (e.g. excluding a covariate or including too many covariates). However, the exclusion of unmatched treated participants (and possibly unmated controls) can decrease the precision of the estimates [203, 209, 210]. The major advantage of PS stratification is that it includes all available study subjects and therefore, increases the precision of the estimates and is, again, robust to misspecification. The main disadvantage of this method is that, despite the fact that the division of the propensity scores into five strata has been shown to eliminate 90% of the bias from measured confounders, stratification reduces bias less than other methods [203, 209, 211, 212]. As in PS stratification, covariate adjustment uses all included study subjects. However, this technique is not considered ideal for several reasons. The model produces odds ratios and hazard ratios but does not allow estimate of absolute treatment effects such as risk difference and numbers needed to

treat and has been show to produce more biased estimates of these ratios. Additionally, the assessment of balance in baseline covariates between treatment groups is more cumbersome than other methods [203, 212-214]. And finally, while IPTW reduces bias more than stratification and covariate adjustment, misspecifcation in the propensity-score model may have a substantial impact on the weights applied and therefore, can become unstable [203, 209, 211, 212].

The large number of covariates in our data that were required to be included in the propensity-score model, the recognised robustness of PSM, the fact that PS stratification allowed for all data to be included in the analysis and given that both of these methods are the most commonly reported methods in published literature resulted in the application of these two methods in our observational dataset [215-217].

Covariates were selected for inclusion following a review of the literature and consultation with clinicians [218-222]. Prior knowledge of covariates that impact the outcome is important. Only covariates that simultaneously influence the treatment assignment and the outcome should be included. There is debate over the impact of including too few or too many variables in the estimation of the PS with some suggesting that it may impact the variance around the outcomes but there is universal agreement that the choice of variables should be based on previous findings and expert advice [223, 224].

For each method, the relative balance in measured baseline covariates is compared using the standardised difference [204]. The standardised difference compares the mean of continuous and binary variables between treatment groups [203]. The advantage of using the standardised difference is that, unlike significance testing, it is not affected by

sample size. To assess the balance in covariates after PS matching, the balance in measured baseline covariates between treated and untreated subjects within the PS matched sample were compared for all three approaches using standardised differences. For stratification, within-strata standardised differences are computed to compare the distribution of baseline covariates between treated and untreated subjects within the same PS stratum. The mean standardised difference is then determined across the strata [204]. Although there is no universal criterion as to what threshold of standardised difference can be used to indicate important imbalance, a standardised difference that is less than 0.1 has been taken to indicate a negligible difference in the mean of a covariate between treated and untreated subjects [203].

3.2.3.3 Multiple Imputation

Missing data are unavoidable in clinical research [225]. Missing data refers to unrecorded values, which, if recorded, would be meaningful for the analysis and interpretation of a study [226, 227]. It can pose a threat to the validity of observational outcome analysis [228]. The intent of any analysis is to make valid inferences from the data, and therefore, meaningful assessment of patients' outcomes in observational studies requires a reliable and accurate measure of the outcome itself.

Researchers have often addressed missing data by including only complete cases in the analysis – those individuals who have no missing data in any of the variables required for the analysis. However, this often leads to the exclusion of a substantial proportion of the original sample, which in turn causes bias, loss of precision and power [225]. The risk of bias due to missing data depends on the reasons why data are missing.

3.2.3.4 Dealing with Missing Data

Given that nearly all statistical methods presume complete information for all variables included in the analysis, it is essential that appropriate methods are employed to deal with missing data [229]. It is possible to distinguish between two patterns of missingness. Data is missing monotone if a pattern is observed among the missing values. Data is missing arbitrarily if there is no way to order the variables to observe a clear pattern (Figure 12).

Missing monotone				Missing arbitrarily			
v1	v2	v3	v4	v1	v2	v3	v4
X	X	X	X	X	X	.	X
X	X	X	X	.	X	X	.
X	X	X	.	X	.	X	.
X	X	.	.	X	X	.	.
X	.	.	.	.	X	X	X

Figure 12: Patterns of missingness
Sourced by Soley-Bari [229]

Statistical imputation techniques should be used to estimate or approximate missing data by modelling the characteristics of cases within missing data to those who have such data. There are several methods to deal with missing data, including *ad hoc* methods such as case-finding, case deletion, mean substitution and more principle methods such as maximum-likelihood methods, multiple imputation (MI) and others. When it is plausible that data are missing arbitrarily, analysis based on complete cases may be biased. Such biases can be overcome using methods such as MI that allow individuals with incomplete data to be included in the analysis [230]. In this thesis, we will employ the MI methodology to deal with missing data, where appropriate.

The goal of MI is to provide valid inference in scenarios in which the data is incomplete and when reasons for missing values are not known. One of the basic objectives of MI is to enable the inclusion of complete-data in the analysis [230]. MI is a general method that incorporates the uncertainty into the imputation process. MI is comprised of three stages: imputation stage, in which missing data are imputed; analysis stage, in which each complete dataset is analysed using complete-data technique; and the last stage, in which the results from the analysis are combined in order to yield a final result that combines the uncertainty in the data and the uncertainty due to missing values. During the imputation stage, imputed values are drawn from a distribution, and therefore inherently contain some variation. Thus it solves the limitations of single imputation by introducing an additional form of error based on variation in the parameter estimates across the imputation. It replaces each missing value with two or more acceptable values, representing a distribution of possibilities [225].

The advantages of this method are [231-233]:

- It produces unbiased estimates of standard error and thus ultimately helps to preserve original available data distribution, providing more validity than ad hoc approaches to missing data.
- It uses all available data, preserving sample size and statistical power.
- It introduces random variation, which enhances the possibility to have unbiased estimates of all parameters.
- The results are readily interpretable.
- It is suitable for dealing with data missing arbitrarily.

3.3 Registries

Real world data can be accrued through prospective cohort studies and a registry is an established method for this type of study. A registry is a form of cohort study that

follows a large population of patients recruited with a specific disease and are used extensively to study the natural history of a condition, the predictors of key outcomes and effectiveness of treatments [234]. The basic description of a registry is an observational, non-experimental database designed to reflect current patterns of practice without influencing the treatment or intervention being described [9]. A treatment registry is designed to collect all cases of a particular disease or condition treated with a specified intervention or therapeutic class of drugs. The Agency for Healthcare Research and Quality defines a patient registry as 'an organized system that uses observational study methods to collect uniform data (clinical or other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes' [226]. A patient registry can be a powerful tool to observe the course of disease, to understand variations in treatment and outcomes, to examine factors that influence prognosis and quality of life, to describe care patterns including appropriateness of care and disparities in the delivery of care, to assess effectiveness, to monitor safety and harm and to measure quality of life [226].

The potential for registries to collect real world data is considerable. A registry can address clinical questions on effectiveness, safety and compliance, information on disease and/or treatment-specific changes in qualify of life, and address regional and national variations in treatment patterns [9]. Registry studies are often referred to as real world studies, to distinguish them from clinical trials [235]. Many observational databases worldwide, most of which are electronic, were borne out of business process needs (e.g. claims databases); however, provider-led databases focusing on a specific disease and/or patient population have emerged [236]. Database sources for observational studies that currently exist are heterogeneous in terms of the type of patient populations followed, data elements collected, geography and funding

mechanisms. Claims databases have the advantage of being large and capturing almost every interaction within the healthcare delivery system. However, because these data are used for claims and billing purposes, they lack detailed and complete clinical information. In addition, these databases make it difficult to differentiate between comorbid conditions and complications of care and they may only capture specific geographic markets or represent a subpopulation. On the other hand, clinical databases, although smaller, have the advantage of containing more detailed clinical data. However, their accuracy and completeness are dependent on the individual responsible for data entry [236]. In general, databases are only as useful as the quality of the information that is collected, where the adage “bad data in, bad data out” applies. The quality of the data and completeness can vary dependent on the source of data and assurance measures implemented. Missing, incorrectly coded and incomplete data can be problematic when developing an analytic dataset and the results are only valid if these problems are limited.

The importance of registries is increasingly recognised as they are used more frequently to fill important gaps in evidence and contribute to understanding how trial results can be applied in practice [235]. Data from registries are also used to support timely decisions by regulatory agencies about safety. Information regarding patient characteristics, comorbidities, risk factors, treatment patterns and outcomes can be assessed. Observational registry data can be synergistic with RCTs for effectiveness evidence development [237]. Alternatively, these data can be used to confirm the generalisability of RCT findings among a broader spectrum of patients and providers. Beyond consideration of therapeutic effectiveness and safety, registry data can also be used to assess the incremental healthcare costs associated with one treatment versus its comparator and can provide a broader and more accurate measure of true costs of treatment in real world practice [15, 236].

Registries, claims-type databases and provider-led databases, offer the opportunity to provide insights into the outcomes and costs of existing and even new therapies by leveraging observational databases to inform decision-making. These registry datasets can address the effectiveness of therapies as they are used in practice, providing valuable insights into real world safety and costs [236].

3.3.1 Classification of Patient Registries

The breadth of studies that can be included as patient registries is large. Patients included in a registry, are typically selected based on a particular disease, risk factor or exposure. Three general categories account for the majority of registries developed for evaluating patient outcomes. These include observational studies in which the patient has an exposure to a product or service, has a particular disease or risk factor or various combinations thereof [226].

3.3.1.1 Product Registries

In this type of registry, the patient is exposed to a healthcare product, a drug or a medical device. Exposure may be brief (i.e. single dose) or may be for long-term use. They provide a mechanism for monitoring the long-term safety and effectiveness in the 'natural environment' [238].

3.3.1.2 Disease Registries

A disease registry is a patient registry that tracks outcomes in a population of patients who have the same diagnosis (e.g. HCV infection) or who have undergone the same medical procedures. They can be used to estimate disease prevalence and incidence, to estimate healthcare resource utilisation and clinical outcomes and to track changes in these parameters over time [239]. They may also serve as data sources for conducting comparisons in healthcare utilisation and outcomes from different categories of patients, for example, according to ethnicity, gender, age or geographic areas. They

allow for estimations of the demand for health services and may serve as sampling frames for selecting patients who fulfil specific study eligibility criteria. The use of disease registries is particularly beneficial for diseases affecting very small populations and for looking at specific populations, such as children [240].

3.4 Evidence Synthesis

Evidence based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [241]. Clinical decisions should be based on the totality of available evidence, rather than based on the results of any individual study or trial [242]. It is not restricted to randomised trials and meta-analyses; it is the finding of evidence and using that evidence to make clinical decisions. A cornerstone of EBM is the hierarchical system of classifying evidence. This hierarchy is known as the levels of evidence [165]. In the hierarchy of research designs, the results of RCTs are considered to be evidence of the highest grade, whereas observational studies are viewed as having less validity because they reportedly overestimate treatment effects [243] (Figure 13).

Figure 13: Hierarchy of evidence
This pyramid appropriately represents the levels of evidence
Sourced from Golden et al [244]

The debate surrounding evidence to support therapeutic use has become particularly apparent with the emergence, over the past thirty years, of hierarchies of evidence [12]. This approach to evidence has not only been adopted by many in the EBM and HTA movements, but it has also come to dominate the development of clinical guidelines.

Evidence synthesis aims to obtain a comparison, for purposes of efficacy and/or cost-effectiveness, of a specific set of treatments in patients with pre-specified characteristics. This is the level at which reimbursement authorities now typically operate and in which clinicians are interested [245]. Over the last two decades we have experienced the EBM revolution in how interventions are evaluated and administered. Central to this initiative is the use of systematic reviews, since it is accepted to be the highest level of evidence regarding effectiveness of interventions [246].

Decision-makers, HTA agencies and physicians now require a comprehensive range of well-designed studies, RCTs, single-arm trials, observational studies etc., to support prescribing and reimbursement decisions [11, 13]. Decision-makers are required to assess and appraise all the available evidence irrespective of whether it has been derived from RCTs or observational research. A comprehensive evidence base is essential for making balanced judgements about the management of diseases. RCTs should, and will, remain a key part of clinical research. However, observational studies should serve as a complementary, not rival, technique in clinical practice. When combined, the data can provide a comprehensive evidence base for clinical decision-making [12, 13]. Increasingly, governments and payers are using evidence-based reviews to inform medical decision-making, plan future research agendas, and establish clinical policy. Timely useful evidence from the biomedical literature should be an integral component of clinical decision-making [247, 248].

At the top of the hierarchy of evidence is a systematic review (Figure 13), which also encompasses meta-analyses and network meta-analysis (NMA). A systematic review is “a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies” [249]. A rigorous review conducted according to the established guidelines can address important clinical questions that cannot be fully answered by RCTs alone, and can be a powerful tool in evidence synthesis [244]. Systematic reviews of RCTs are considered the standard basis for evidence-based healthcare decision making for clinical treatment guidelines and reimbursement policies [250].

In the HCV landscape (and in many other disease areas), where a myriad of treatment options are available, there is often an absence of head-to-head RCTs. This prevents consensus as to which agent has the highest rates of treatment response. Thus, in the absence RCTs involving direct comparisons of all treatments of interest, mixed treatment comparisons (MTCs) and NMAs provide useful evidence for judiciously selecting the best choice or choices of treatment [250, 251, 252]. These estimates of relative efficacy will be of use to decision-makers involved in cost-effectiveness assessments, and to clinicians when considered along with clinical parameters in the setting of individual patient treatment pathways [253].

3.4.1 Meta-Analysis

Meta-analysis is a statistical procedure that integrates the results of several independent studies considered to be 'combinable' [252, 254]. It provides a potential solution to the problem of deciding between treatments that have not been directly compared [254-256]. Direct comparisons involve a meta-analysis combining the results of multiple trials that all compare the treatment of interest to the same comparator [257]. It involves the computation of summary statistics for each trial followed by the combination of these studies into a weighted average. Well-conducted meta-analyses allow a more objective appraisal of the evidence than traditional narrative reviews, providing a more precise estimate of a treatment effect [254].

Traditional meta-analytical methods pertain to pairwise comparisons between two interventions, thus only partially providing evidence that patients, clinicians, and policy-makers need in order to make informed decisions or public health recommendations regarding prevention, screening, diagnosis and treatment. Recent statistical advances have resulted in the development of methodologies that allow the estimation of efficacy metrics for all possible comparisons in a body of evidence, regardless of whether there

have been direct head-to-head comparisons in clinical trials. These methods are collectively known as NMAs or MTCs and they constitute some of the latest tools in evidence-based medicine for evaluating networks of interventions [258, 259]. These methods are particularly useful in decision-making contexts [260].

3.4.2 Network Meta-Analyses

NMAs expand the scope of a traditional pair-wise meta-analysis by simultaneously analysing both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator [261]. NMAs can form the basis of models used by health economists for their cost-effective analysis, and therefore provide very useful information for clinical and reimbursement decision-making in the absence of head-to-head data [252, 256]. In their simplest form, they combine direct and indirect estimates of relative effect, where indirect evidence refers to evidence on treatment C relative to B obtained from A vs. B and A vs. C studies [262]. NMAs produce an internally coherent set of estimates of the efficacy of any treatment, in the absence of head-to-head comparisons, in the network relative to any other [252, 263, 264]. Although direct comparisons top the hierarchy of evidence, when they are absent the approach of NMAs using indirect randomised data is the best tool for comparing treatments and making recommendations [264].

The standard requirement for the conduct of NMAs is that the network of evidence must be connected. A connected network ensures that all treatments can be connected to one another by one or more paths [265]. Due to recent developments in the treatment of HCV, there is currently an evidence base for NMAs that forms a disconnected network and has provided a significant challenge for estimating the relative treatment effect for HCV therapies in the absence of head-to-head trials. For more than a decade, PR was the standard of care for HCV GT1. With the approval of the first

generation DAAs, TPV/PR and BOC/PR, triple therapy using a DAA/PR combination became the recommended treatment and more recently, dual DAA combinations with or without RBV are recommended. In traditional NMAs, newly initiated RCTs would include either PR or a DAA/PR regimen as a common comparator to connect new regimens to the network. However, following recent FDA/EMA guidance, the efficacy of many DAA agents was assessed using open-label, single-agent studies with historical controls [266]. As a result, the NMA landscape for HCV GT1 is disconnected (Figure 14).

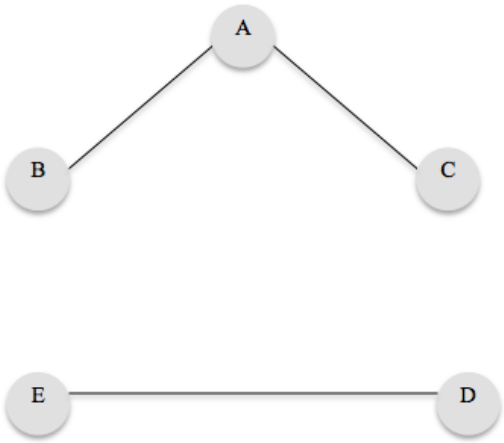


Figure 14: Schematic diagram of a hypothetical disconnected network
Treatments D and E are not connected to the network of treatments A, B and C.

More recently, alternative methods of combining data from different study designs (open-label, non-comparative studies and observational studies) into an NMA have been proposed [267]. These methods differ in their flexibility to adjust for potential bias. One method, naïve pooling, does not differentiate between trial design and simply pools across all trials regardless of their design [267, 268]. It is the simplest approach to combining studies of differing design and does not allow adjustments to be made for potential bias in study design or to downweigh studies of lesser quality. The hierarchical model is a three-level model and accounts for between study design heterogeneity [269]. It introduces a study-type level that accounts for differing study designs. In this model, the treatment effect at each level is combined to give the overall treatment effect (Figure 15).

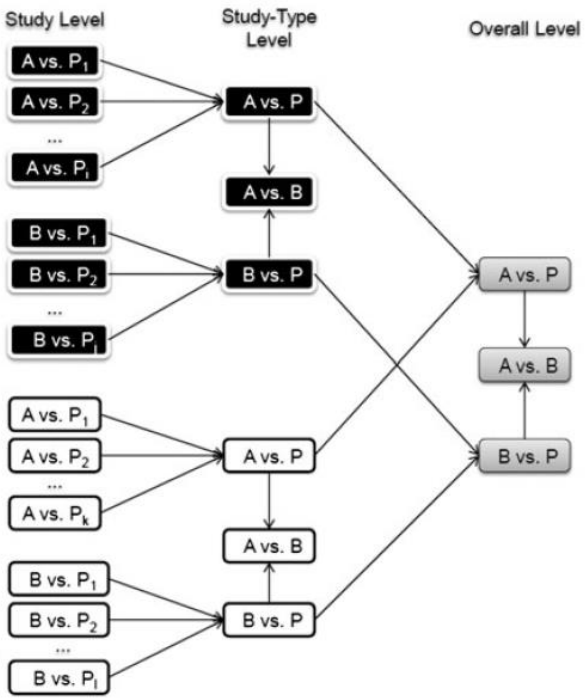


Figure 15: Schematic representation of the three-level hierarchical model
In this NMA, trials comparing drug A and placebo (P) are combined with trials comparing drug B and P. Evidence from different trial designs is colour marked: black refers to RCTs and white refers to observational trials. Evidence from trials of the same design is combined to study type level estimates. Study type estimates are then combined to obtain overall estimates (grey)
Sourced from Schmitz et al [267]

The hierarchical model is the most flexible approach to including different forms of evidence. It allows for adjustment to be made for systematic bias and for the down-weighting of different trial designs.

There are two roles for the NMAs: one is to strengthen inference concerning the relative efficacy of two treatments, by including both 'direct' and 'indirect' comparisons. The other is to facilitate simultaneous inference regarding all treatments, in order to select the best treatment [270]. They have great potential for estimating the comparative-effectiveness of multiple treatments using an evidence base of trials that individually do not compare all treatment options. When connected networks of evidence are synthesised simultaneously, they provide estimates of the comparative effectiveness of

all included treatments and a ranking of their effectiveness with associated probability statements.

Two advantages for considering all the evidence in the NMA model are [271]

- It allows the inclusion of all the evidence, which will reduce the uncertainty in the pooled estimate of interest
- It allows us to formally check the consistency of the evidence

Different methodologies have been described for NMAs; one such method uses Bayesian principles [251]. A Bayesian approach to statistical inference has been referred to as "the explicit quantitative use of external evidence in the design, monitoring, analysis and interpretation of a healthcare evaluation" [10]. Bayesian statisticians express their belief about the size of an effect by specifying some prior probability distribution before seeing the data, and then they update that belief by deriving a posterior probability distribution, taking the data into account [254]. A Bayesian NMA model provides a powerful methodology to obtain estimates of relative treatment effect when head-to-head evidence is not available or insufficient [267].

A major advantage of the Bayesian approach is that the method naturally leads into a framework that supports decision-making. Other advantages of a Bayesian meta-analysis include the straightforward way of making predictions, and the possibility of incorporating different sources of uncertainty [252, 272]. One disadvantage is that the computations required in the Bayesian models are very complex and the expression of prior beliefs in a form which can be included in analysis is a non-trivial task [255].

Most NMAs to date use the Bayesian WinBUGS software. While, for statisticians, it is the most straightforward method of combining the direct and indirect evidence, it is limited in functionality and accessibility to the non-statistician [261]. Using Bayesian Markov Chain Monte Carlo methods it is possible to rank all treatments and produce a probability that any one treatment is the 'best'. This is a powerful illustration of the ability of Bayesian statistical methods to make direct probability statements about quantities of central interest to a decision [10, 271].

To conclude, systematic reviews, meta-analyses and NMAs, being at the intersection of clinical medicine, epidemiology, statistics and translational research, are key methodologies for the practice of EBM, and should include all available evidence, both RCTs, single-arm studies and observational studies [258]. However, the quality of this evidence is a function of the quality of the primary studies available as well as the degree of rigor to which the systematic reviews have been performed. A poorly completed systematic review and meta-analysis or NMA may give rise to misleading results and conclusions when using methods and statistical approaches that may lack credibility [242].

3.5 The Irish Hepatitis C Outcomes Research Network

When new drugs receive their marketing authorisation, particularly those with high acquisition costs and with questions surrounding their affordability and budget impact, it is invaluable to prospectively collect information on treated patients in the clinical setting to allow assessment of the benefits and perhaps, the emergence, or incidence, of AEs that were not identified in clinical trials.

The introduction of the first generation protease inhibitors for use in combination with PR in 2012 represented a significant advance in the treatment of HCV GT1. However, these treatment regimens came with additional costs and side effects. The availability of these therapies represented an opportunity to maximise the stewardship of the therapeutic management of HCV in Ireland to ensure optimal clinical and economic outcomes from the use of new agents to the market. Thus, in 2012, the Irish Hepatitis C Outcomes Research Network (ICORN) was established. The goal of the collaboration was to optimise the quality of care of HCV-infected patients treated with DAA therapy. This included the design and implementation of treatment protocols and the establishment of a national treatment registry. ICORN is an interdisciplinary, interagency network comprising of hepatologists and infectious disease consultants, virologists, epidemiologists, patient representatives, pharmacists, nurses and health economists. All seven hospitals with centres of excellence in gastroenterology, hepatology or infectious disease treating patients with HCV infection are involved. Additionally, ICORN has developed partnerships with with the NCPE, HSE and the Department of Health (DoH).

ICORN developed the protocol for a prospective, longitudinal, observational outcomes research study for patients with HCV treated with DAAs and additionally developed a national HCV registry, which commenced in June 2012. The registry represents a comparative effectiveness observational study aimed at collecting clinical and economic real world data for patients with HCV treated with DAA therapies to better establish their effectiveness and safety in the real world clinical environment. It assesses and records treatment outcomes using data from real life clinical practice. It was the first prospective clinical and economic outcomes registry to be developed with multidisciplinary involvement from clinicians and healthcare providers in Ireland.

3.5.1 Process of Development of the HCV registry

A registry research protocol was developed using best-practice guidance on observational research studies [167, 226, 273, 274]. The study design is an on-going, multi-centred, prospective, longitudinal, observational outcomes research study. The aim of this research study is to:

- Determine the effectiveness, safety and tolerability of HCV DAA therapy in the real world Irish setting
- Compare the clinical trial outcome data with the real world effectiveness data
- Assess the total costs associated with treating HCV patients with DAA therapy and consequently the budget impact

Ethical approval was obtained from the St. James' Hospital/Tallaght Research Ethics Committee. All patients eligible for inclusion in the HCV registry must sign a patient consent form prior to initiation of therapy. Consistent with data protection requirements, no identifiable patient information is entered into the registry database.

Patients are eligible for inclusion in the registry if they meet the following criteria:

- HCV treatment naïve patients
- HCV treatment-experienced partial responders, relapsers (defined as undetectable HCV-RNA at the end of therapy but had subsequent detectable HCV RNA at, or after, 12 weeks follow up) and null-responders
- Patients with and without the presence of cirrhosis
- HCV/HIV co-infection
- Adult patients ≥ 18 years

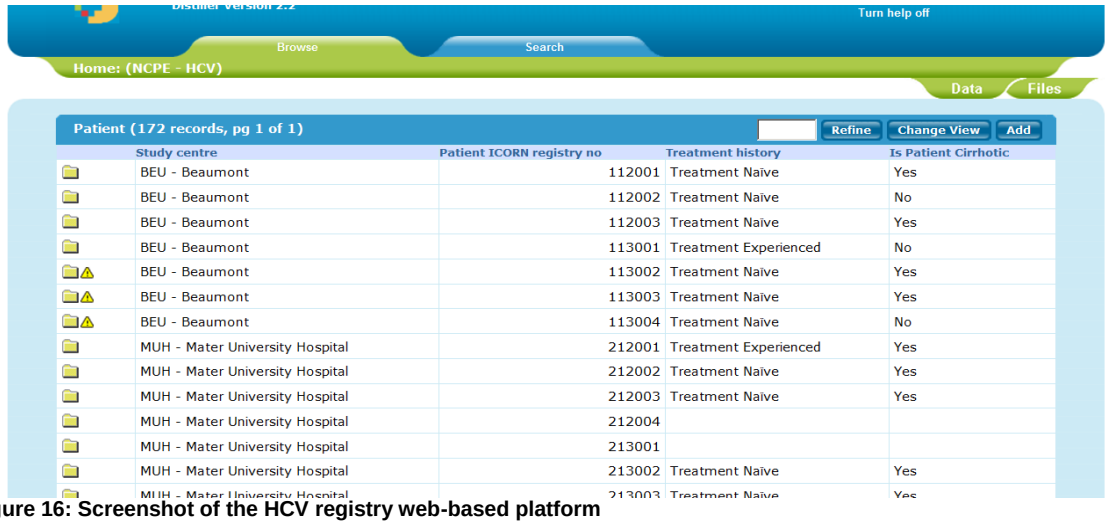
Patients are excluded from the registry if they meet any of the following criteria:

- Pregnant and breast-feeding women
- Children < 18 years
- Alcohol dependent patients

Clinicians or clinical nurse specialists (CNSs) in the seven centres of excellence recruit patients. Recruited patients are assigned a treatment registry number and anonymised data is entered into the database.

3.5.2 Development of the Web-Based Platform for Patient Data Collation.

The HCV registry is a web-based tool hosted on an electronic platform developed by the Dublin Centre for Clinical Research (DCCR) in conjunction with ICORN (Figure 16). It is a robust data management tool that supports the collation of patient level data. The platform is a protected and secure cloud-based system that conforms to all appropriate security considerations for clinical research. The tool is an integrated system for collecting, cleaning, storing, monitoring, reviewing and reporting of patient level data. A minimal dataset of patient variables was developed to translate the research questions into measurable outcomes. A process of consultation and piloting was undertaken to determine the final dataset and to build and adjust the web-based registry platform in order to maximise performance.



Study centre	Patient ICORN registry no	Treatment history	Is Patient Cirrhotic
BEU - Beaumont	112001	Treatment Naïve	Yes
BEU - Beaumont	112002	Treatment Naïve	No
BEU - Beaumont	112003	Treatment Naïve	Yes
BEU - Beaumont	113001	Treatment Experienced	No
BEU - Beaumont	113002	Treatment Naïve	Yes
BEU - Beaumont	113003	Treatment Naïve	Yes
BEU - Beaumont	113004	Treatment Naïve	No
MUH - Mater University Hospital	212001	Treatment Experienced	Yes
MUH - Mater University Hospital	212002	Treatment Naïve	Yes
MUH - Mater University Hospital	212003	Treatment Naïve	Yes
MUH - Mater University Hospital	212004		
MUH - Mater University Hospital	213001		
MUH - Mater University Hospital	213002	Treatment Naïve	Yes
MUH - Mater University Hospital	213003	Treatment Naïve	Yes

Figure 16: Screenshot of the HCV registry web-based platform

The variables chosen for collection were determined by the outcomes of the study. Moderators of treatment outcomes were specifically targeted for inclusion [275, 276]. This data was obtained from a literature review and clinician input. The need to ensure a minimal dataset was deemed a priority to avoid capturing data not required and to create a clean database for analysis [277]. Consultation with a biostatistician was undertaken. The variables at baseline were divided into categorical and continuous variables and stratified into baseline characteristics, HCV-related data and laboratory data (Table 5).

Table 5: Sample of both categorical and continuous variables collected in the registry

	Categorical Variables	Continuous Variables
Baseline demographic data	Gender	Age
	Smoking status	Weight
	Past alcohol use	Height
	Co-morbidities	
	Country of birth	
	County of residence	
	Ethnicity	
	Employment status	
	Medications	
HCV-related data at baseline	Acquisition risk factor	
	Treatment choice	
	Treatment history	
	Stage of liver disease	
	Genotype	
	IL28B Allele	
Laboratory data		HCV-RNA (IU/ml)
		Serum albumin (g/L)
		ALT (IU/ml)
		Total bilirubin (µmol/L)
		Platelet Count ($x10^{-9}$/L)
		White cell count ($x10^{-9}$/L)
		Alpha fetoprotein (IU/L)
		INR

The definitive clinical outcome data for patients treated is the SVR12 or SVR24 [83]. Additional clinical outcome data for analysis includes:

- End-of treatment HCV-RNA
- Discontinuation rates
- Dose reductions
- Medications prescribed for the management of AEs
- Liver disease progression

3.5.3 Data Collection and Retrieval

Designated data collectors manually extract data at each site through chart review to facilitate collation of patient level data. Site visits are facilitated through arrangements

with CNSs at each site. Data is captured on specifically designed data collection sheets that mirror the registry data inputs. Manual data collected at site visits is entered into the registry in preparation for data retrieval and analysis.

The registry allows data to be extracted on an individual, site specific or a pooled total patient cohort basis. Categorical variables in the registry are retrieved in narrative format. Data for extraction is downloaded into a Microsoft Excel workbook in a narrative formation. Using a codebook developed for the HCV registry, categorical narrative data is coded. Continuous variables are extracted as per data entry. The data then undergoes a systematic quality control process prior to analysis.

3.5.4 Quality Control

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) defines quality control as 'the observation techniques and activities used to fulfil requirements for quality [227, 278]. The quality of data within the registry is of integral importance and is a key aspect of the work of ICORN operations and those involved in data analysis.

The potential problems with regard to the quality control of the data from the HCV registry include the following:

- Missing data
- Anomalous/implausible data (often continuous variables) – usually attributable to errors in data recording and input

Data cleaning, as an essential aspect of quality assurance and a determinant of study validity, should adhere to good practice guidelines for data management and require

transparency and proper documentation of all procedures [279]. Data cleaning deals with data problems once they have occurred. Error prevention strategies can reduce many problems but cannot eliminate them. Using van den Broeck *et al* as a seminal guide to data cleaning, a three stage data cleaning process has been adopted, involving repeated cycles of screening, diagnosing, and editing of suspected data abnormalities [227].

As discussed previously, missing data refers to unrecorded values, which, if recorded, would be meaningful for the analysis and interpretation of a study [226, 280]. It is a common problem in any clinical registry, and poses a threat to the validity of observational outcomes analyses [228]. The intent of any analysis is to make valid inferences from the data and observational studies can be open to data that is missing, not recorded or not undertaken. Meaningful assessment of patients' outcomes in observational studies requires a reliable and accurate measure of the outcome itself. Strategies for identifying and assessing the quantity of missing data have been adopted.

Anomalous data is data that results from errors, such as typing errors, or represents unusual events [279]. These are values in the database that represent data that fall outside a plausible range (outliers). Sources of errors are multifactorial and often relate to human error. The sources of potential errors in recording data in the HCV registry include the following:

- On site recording of data in charts/nursing notes
- At the point of recording in data collection sheets
- At the point of data entry into registry

Good practice on data cleaning recommend a three phased approach of repeated cycles of screening, diagnosis and correction i.e. editing of suspected data abnormalities [279]. The data cleaning process gives an insight into the nature and severity of error generating processes. This methodological feedback is given to operational staff to improve study validity and precision of outcomes. The feedback can result in amendments to the study protocol, regarding design, data collection and quality control procedures.

The quality control processes undertaken by registry analysts are dependent on the type of data or problem encountered. For categorical data, a process of double data entry is undertaken. This is done on a random selection of patients. For continuous data, individual patient variables will undergo range and frequency checks to identify errors, true extreme, true normal or idiopathic. Subsequent validation of the data will be undertaken through a validation/verification process at each site.

Following completion of the quality control procedures, the registry data is corrected if errors are true and correct values obtained, deleted if determined to be true errors that will impact on study outcomes or where data cannot be verified, and retained if seemingly implausible data, is in fact true.

3.5.5 Data Analysis

Data is analysed in accordance with best-practice guidance [199, 281]. The data required and methods of analysis will be dependent on the objectives of the individual studies. For this thesis, the methods of analysis will be outlined for each study separately.

Chapter 4

Chapter 4 Do Disparities Between Patient Populations in Randomised Controlled Trials and the Real World Lead to Differences in SVR rates? A Systematic Review

4.1 Introduction

The breakthrough therapy designation (BTD), was established by the US Congress and the Food and Drugs Administration (FDA) in 2012 and adopted by the EMA in 2016 to expedite the development of drugs that show promising early clinical evidence of benefit over available therapies [282, 283]. In the case of HCV, SOF, SOF/DCV±RBV, SOF/LDV±RBV and 3D±RBV were all designated as breakthrough therapies having demonstrated the potential for significantly improved efficacy and tolerability [284]. The clinical trial programmes supporting product licensing for these IFN-free regimens involved both comparative and non-comparative trials. Evidence of efficacy in certain subpopulations of patients with HCV infection (genotype, presence of cirrhosis, decompensated cirrhosis etc.) was limited by small patients numbers and strict inclusion criteria and limited generalisation of outcomes to the real world clinical setting.

When designed appropriately, clinical trials report treatment efficacy, a measure of the capacity of a treatment to produce the desired effect in a controlled environment [285-287]. Treatment outcomes in routine clinical practice may be modified by concomitant co-morbid medical conditions, substance abuse, poor adherence and loss to follow-up, resulting in potentially lower effectiveness rates than those obtained in clinical trials. It is important to evaluate how trial efficacy translates to real world effectiveness [288]. Observational comparative effectiveness studies allow estimates of treatment effectiveness to be determined [285].

Following the availability of the breakthrough treatment regimens for HCV infection, a number of collaborative research networks were formed to conduct comparative effectiveness observational studies for patients treated under their care [289-291]. These studies are designed to determine real world effectiveness and to compare results with the clinical trial data.

The aim of this study was to conduct a systematic review of the published literature to report and compare the outcomes in RCTs and observational studies of DAA treatment regimens licensed for use in GT1 HCV-infected individuals and to investigate possible reasons for any disparity between efficacy and effectiveness. The review was limited to treatment combinations for GT1 HCV for two reasons. First, GT1 is the most prevalent genotype in HCV-infected individuals globally, accounting for 46% of all infections, and in Ireland (55%) [5, 51]. Second, in both the AASLD and EASL guidelines, GT1 individuals have the widest array of treatment options available [7, 122].

4.2 Methods

This systematic review was conducted in accordance with the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (PRISMA) [292].

4.2.1 Search Strategy

Using a pre-defined search strategy, along with pre-specified inclusion criteria incorporating the PICOS (Population, Intervention, Comparator, Outcome and Study Design) structure for formulating a research protocol [293], an electronic literature search in PubMed, EMBASE and The Cochrane Database of Systematic Reviews was systematically performed on May 6th 2015, for comparative and non-comparative clinical trials, and July 9th 2015, for observational studies (Table 6). Both searches were

repeated on Nov 24th 2015. The search included all studies published up to Nov 24th 2015*. Details of the search strategy can be found in Appendix 1. In order to reduce the effect of publication bias, a hand-search of conference abstracts, for both clinical trials and observational studies, from the AASLD and EASL conferences between 2010-2015, was performed. The bibliographies of identified articles were also hand-searched for potentially relevant articles.

4.2.2 Eligibility Criteria

RCTs, non-comparative clinical trials and observational studies were included if the patient population consisted of HCV GT1-infected individuals (over 18 years of age) treated with one of the EMA approved treatment combinations. Inclusion and exclusion criteria are outlined in Table 6. Criteria specified that SVR12, or SVR24, must have been included as a primary or secondary endpoint. Dose-finding studies, studies presenting information exclusively about acute or non-GT1 HCV, and studies that included HIV co-infected patients were excluded.

* Two abstracts identified during this period that met all inclusion criteria were subsequently published as full text articles in early 2016 and thus, are referenced as such.

Table 6: PICOS criteria used in the search strategy for RCTs and observational studies

Inclusion criteria	**Details**	**Comments**
Patient population	HCV genotype 1 patients > 18 years	
Intervention(s)	Telaprevir, Boceprevir, Simeprevir, Sofosbuvir, Ledipasvir, Daclatasvir, Paritaprevir, Ombitasvir, Dasabuvir	Includes any licensed combinations of these drugs
Comparison therapy	Any comparator or non-comparative studies	
Patient outcomes	SVR12, SVR24	
Study types	Randomised/non-randomised, comparative/non-comparative clinical trials, observational/real world studies	Includes open-label, single-arm and single-agent studies
Publication type	Full text journal articles, conference abstracts reporting SVR outcomes	
Limits	Humans	
Exclusion criteria	**Details**	**Comments**
Patient population	Non-genotype 1 patients, < 18 years, HIV co-infection, HBV co-infection, patients post orthotopic liver transplant	
Intervention(s)	Unlicensed drugs/drug combinations	
Comparison therapy	No limits	
Patient outcomes	Not reporting SVR	
Study types	Not randomised/non-randomised, comparative/non-comparative clinical trials, observational/real world studies	
Publication types	Comments, editorials, letters	

SVR = sustained virological response, HBV = hepatitis B

4.2.3 Screening and Selection

The screening and selection process is outlined in Figure 17 and was undertaken by two reviewers. Search results from the electronic databases were transferred into the EndNote© referencing system. Due to the overlap in coverage of the electronic databases, there were a large number of duplicate citations that were excluded at this point. Initial screening of the title and abstract (if necessary) was conducted to exclude articles deemed not relevant. Articles that matched the inclusion criteria or those where the abstract did not provide sufficient information to include, or exclude, were selected for full-text review. These articles were then reviewed further for their relevance against the inclusion criteria by reading them in full text. Studies that met the eligibility criteria were included in this study.

4.2.4 Data Extraction

A specifically designed data collection tool was used to extract patient and study characteristics from included studies. If data were unavailable in published material, supplemental appendices were examined. If further data was required, additional information was sought by directly contacting corresponding authors. Data were extracted on the number of patients in each trial arm, the experimental and comparator regimens and relevant baseline demographics and clinical characteristics of patients including gender, GT1 subtype, presence of cirrhosis and previous treatment history. In addition, baseline viral characteristics such as viral load were also extracted. The primary outcome measure was SVR12/24, calculated on an 'intent-to-treat' basis with all patients starting treatment contributing to the denominator.

4.2.5 Risk of Bias Assessment for Randomised Controlled Trials

The quality of included clincal trials was individually assessed by two reviewers using the 'Risk of Bias' Tool in the Cochrane Collaboration software Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) [294]. Each study was assessed for bias by the author under the following domains:

- Random sequence generation (Selection bias)
- Allocation concealment bias (Selection bias)
- Blinding of participants and personnel (Performance bias)
- Blinding of outcome assessment (Detection bias)
- Incomplete outcome data (Attrition bias)
- Selective reporting bias (Reporting bias)
- Other bias (This included consideration of study authors conflicts on interests or whether they were a receipient of funding from the trial sponsor)

4.2.6 Risk of Bias Assessment for Observational Studies

Of the available tools to assess methodological quality in non-randomised observational studies, the Newcastle-Ottawa Scale (NOS) was selected based on recommendation by the Cochrane Collaboration [294, 295]. The NOS scale is restricted to assessment of nine items, categorised into three dimensions including selection, comparability and outcome [296]. For each item, a series of response options are provided. A star system allows a semi-quantitative assessment of study quality. The study is judged on three broad perspectives: the selection of study groups, the comparability of study groups and the ascertainment of the outcome or exposure of interest. The total number of stars that can be achieved in a study is 9, indicating a complete absence of bias. NOS scores are categorised into three groups: very high risk of bias (0 to 3 NOS stars), high risk of bias (4 to 6 stars) and low risk of bias (7-9 stars) [297].

4.3 Statistical Analysis

For each treatment regimen, the clinical trial and observational study data was pooled and tabulated in terms of gender and key HCV characteristics. The SVR12/24 rates from all studies matching the inclusion criteria were recorded. Descriptive statistics were used to describe the HCV characteristics and SVR rates for the study population. Categorical variables were reported as frequencies and percentages. Univariate analyses were performed using the chi-square test as appropriate. A p-value <0.05 was considered to be statistically significant. A sensitivity analysis was performed whereby both clinical trials and observational studies considered to be at high risk of bias were removed and the analysis subsequently repeated to determine whether the inclusion or exclusion of these studies impact the pooled SVR rates. The analysis was performed using SPSS Version 21® (IBM Corp, Armonk, NY, USA).

4.4 Results

Three thousand, three hundred and seven records were identified from PubMed, EMBASE and conference proceedings. After excluding duplicates, the title and abstract (where necessary) of two thousand, eight hundred and twenty nine studies were reviewed, resulting in the identification of 159 studies for further assessment. These consisted of both full text articles and abstracts from conference proceedings. Following the application of eligibility criteria, 86 studies, which reported the efficacy or effectiveness of ten different treatment regimens, were selected for inclusion (Figure 17).

Ten treatment regimens were identified for the treatment of GT1 HCV infection. Five IFN-based regimens were:

- Telaprevir in combination with pegylated interferon and ribavirin (TPV/PR)
- Boceprevir in combination with pegylated interferon and ribavirin (BOC/PR)
- Simeprevir in combination with pegylated interferon and ribavirin (SMV/PR)
- Sofosbuvir in combination with pegylated interferon and ribavirin (SOF/PR)
- Daclatasvir in combination with pegylated interferon and ribavirin (DCV/PR)

Five interferon-free regimens were:

- Sofosbuvir in combination with ribavirin (SOF+RBV)
- Sofosbuvir combined with simeprevir with or without ribavirin (SOF/SMV±RBV)
- Paritaprevir boosted with ritonavir, ombitasvir and dasabuvir with or without ribavirin (3D±RBV)
- Sofosbuvir combined with ledipasvir with or without ribavirin (SOF/LDV±RBV)
- Sofosbuvir combined with daclatasvir with or without ribavirin (SOF/DCV±RBV)

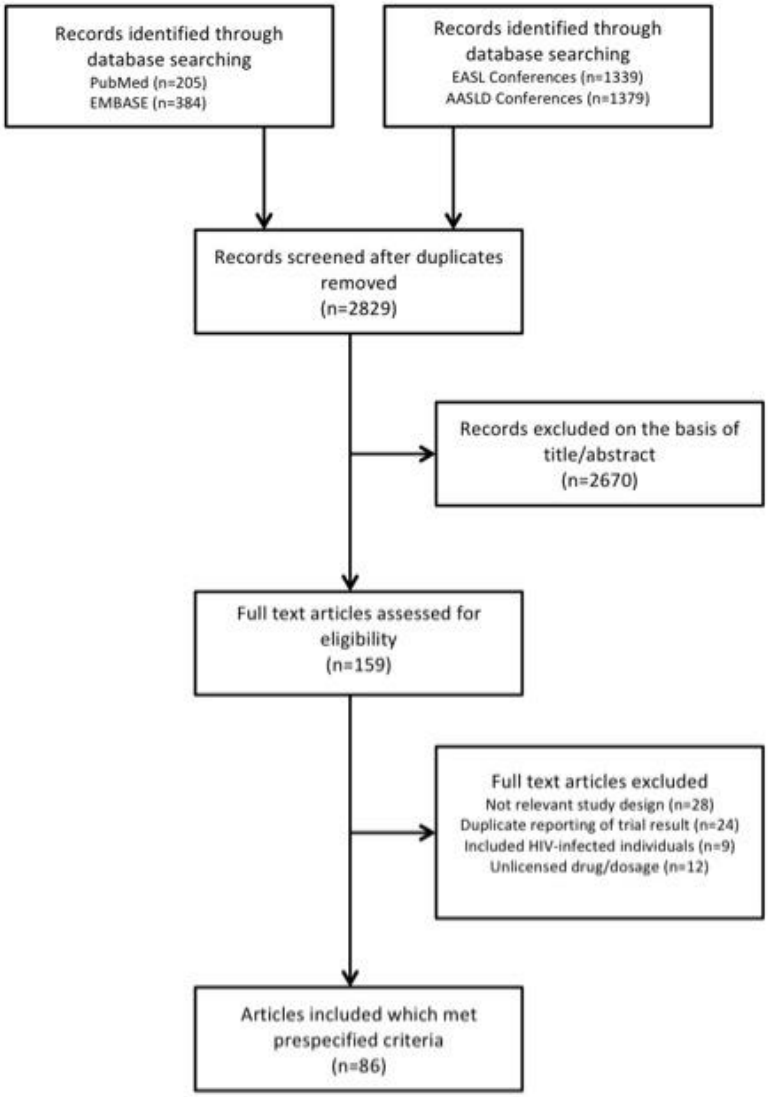


Figure 17: PRISMA flow diagram
Flow diagram depicting studies selected for inclusion

Among the 86 studies, 43 were clinical trials, both randomised and non-comparative studies, and the remaining 43 studies were observational cohort studies [97-105, 110-113, 116-118, 121, 123-130, 157, 289, 290, 298-355]. Characteristics of each of the eligible studies are presented in Appendix 1 Table A 1 and Table A 2. The studies included a total of 40,796 patients of whom 71% were male, 55% were GT1a, 41% had previous treatment experience and cirrhosis was present in 32%. The profiles of the included studies are outlined in Table 7.

Table 7: Profile of randomised controlled trials and observational studies included in the systematic review

	Randomised Controlled Trials	Observational Studies
Studies with no comparator group	23	20
Studies with cirrhotic patients (exclusively)	5	4
Studies with non-cirrhotic patients (exclusively)	16	1
Studies with treatment naïve patients (exclusively)	11	8
Studies with treatment experienced patients (exclusively)	21	3

In the twenty RCTs that included a comparator group, PR was the comparator of choice in seventeen. In the remaining three, the comparators were TPV/PR (n=2) and SOF+RBV (n=1).

Overall, a large population of patients, treated with IFN-based regimens (TPV/PR, BOC/PR, SMV/PR, DCV/PR and SOF/PR), were included in both RCTs and observational studies (n=19,994). However, there were exceptions; a limited number (n=2) of observational studies reported the outcomes for patients treated with SMV/PR and one RCT reported outcomes for patients (n=12) treated with DCV/PR. This treatment regimen was never reported in an observational study (Table 8).

For the five IFN-free regimens (SOF+RBV, SOF/SMV±RBV, 3D±RBV, SOF/DCV±RBV and SOF/LDV±RBV), a substantial number of patients were included in RCTs for 3D±RBV (n=2598) and SOF/LDV±RBV (n=2106). However, for the remaining three regimens, the number of patients included in RCTs was significantly less (SOF/SMV±RBV (n=580), SOF+RBV (n=97) and SOF/DCV±RBV (n=152) (Table 8).

4.4.1 Baseline Characteristics: A Comparison

Four key baseline variables were compared between the RCTs and the observational studies: male gender, previous treatment experience, presence of cirrhosis and the proportion of GT1a patients. The pooled baseline demographics and HCV

characteristics for clinical trials and observational studies stratified according to treatment regimen are presented in Table 8. An analysis was undertaken to evaluate for disparity between RCT and observational study populations. For IFN-based regimens, both RCTs and observational studies were undertaken in four of the five treatment regimens (TPV/PR, BOC/PR, SMV/PR and SOF/PR). A statistically significant difference was observed in the proportion of males and individuals with previous treatment experience, with observational studies comprising of a higher proportion of both than in the RCTs (*p*-value <0.005). Similarly, in TPV/PR, BOC/PR and SOF/PR studies, there were a higher proportion of patients with cirrhosis in observational studies compared to RCTs (*p*=<0.0001). The proportion of patients with GT1a varied for all regimens. With a limited number of patients in the SMV/PR observational studies (n=32), it was difficult to make comparisons with the RCTs for the regimen.

In the IFN-free regimens SOF/SMV±RBV and SOF/LDV±RBV, a statistically significant difference was observed in the proportion of males and individuals with cirrhosis, with observational studies comprising of a higher proportion of both than in RCTs (*p*<0.0001). There was a statistically significant difference in the proportion of patients with cirrhosis between the 3D±RBV RCTs and the observational studies also. In contrast with IFN-based regimens, the proportion of patients with previous treatment experience was lower in the observational studies with statistically significant differences observed in the SOF/SMV ±RBV and SOF/LDV±RBV regimens (*p*<0.0001). The proportion of patients with GT1a varied for all three regimens.

We also examined the countries in which these studies were undertaken. We found that, for both clinical trials and observational studies, the research was completed in developed countries. The majority included populations of patients from North America

and Europe (predominantly Germany, France and the UK) while a small number of studies were undertaken in Asia-Pacific (Japan, Australia and New Zealand).

In general, significant differences in the patient populations included in RCTs and observational studies were identified. Observational studies tended to include a higher proportion of males and a higher proportion of patients with cirrhosis. In IFN-based regimens, the proportion of patients with previous treatment experience tended to be higher in observational studies but this tended to be lower in observational studies reporting outcomes in IFN-free regimens compared with the RCTs.

Table 8: Baseline demographics and HCV characteristics of the clinical trials and observational studies for each treatment regimen after pooling

Treatment Regimen	Study Type	No. of studies included	n	Male (%)	*p-value*	GT1a (%)	*p-value*	Treatment experienced (%)	*p-value*	Presence of cirrhosis (%)	*p-value*
TPV/PR	Clinical trials	7	1813	63.8	0.00012*	53.7	<0.0001*	35.6	<0.0001*	12.2	<0.0001*
	Observational studies	19	7309	86.8		56.8		74.6		46.5	
BOC/PR	Clinical trials	4	1397	62	<0.0001*	60.8	<0.0001*	32.7	<0.0001*	8.3	<0.0001*
	Observational studies	23	7916	89.7		52.5		48.6		33.5	
SMV/PR	Clinical trials	6	1515	61.5	0.004*	45	0.889	55.3	<0.0001*	23.3	0.063
	Observational studies	2	32	89.5		44.8		18.7		9.4	
DCV/PR	Clinical trials	1	12	58.3	-	75	-	0	-	0	-
	Observational studies	-	-	-		-		-		-	
SOF/PR	Clinical trials	3	500	61.2	<0.0001*	77	<0.0001*	0	<0.0001*	58.4	<0.0001*
	Observational studies	4	1717	87.6		62.7		39.2		35.6	
SOF+RBV	Clinical trials	3	97	76	-	79	0.203	0	-	49	0.222
	Observational studies	2	72	N/A		79		0		82	
SOF/SMV±RBV	Clinical trials	3	580	64.1	<0.0001*	77.2	<0.0001*	46.9	<0.0001*	24.8	<0.0001*
	Observational studies	8	3571	80.9		58.4		38.1		61.8	
3D±RBV	Clinical trials	7	2598	57.3	0.936	49.3	0.013*	32.6	0.28	14.6	0.0004*
	Observational studies	2	102	56.8		32.8		27.5		60.8	
SOF/DCV±RBV	Clinical trials	1	152	54	-	80	<0.0001*	27	-	0	-
	Observational studies	3	243	N/A		46		N/A		N/A	
SOF/LDV±RBV	Clinical trials	8	2106	57.7	<0.0001*	64.5	<0.0001*	33.6	<0.0001*	22.2	<0.0001*
	Observational studies	9	5976	71.6		69.1		19.7		39.7	

*Statistically significant, N/A = Not available

4.4.2 Efficacy vs. Effectiveness: A Comparison

The SVR rates for both RCTs and observational studies, following pooling, are presented in Table 9.

4.4.2.1 Interferon-based Regimens

Prior to pooling, the efficacy rates reported for first-generation protease inhibitors (TPV/PR and BOC/PR) ranged from 51%-83% [97-105, 300, 315]. The effectiveness rates were more varied and ranged between 31%-81% [157, 290, 317, 318, 321-324, 327, 328, 332-336, 338-340, 342, 343, 347, 348, 351, 353, 355]. Following pooling, the SVR rate in TPV/PR RCTs was 71% compared to 60% in the observational studies (p<0.0001) with an absolute difference of 11%. In BOC/PR studies, the SVR rate in clinical trials was 64% and 52% in observational studies (p<0.0001) with an absolute difference of 12%.

In second-generation protease inhibitors (SMV/PR, DCV/PR and SOF/PR), the range of efficacy rates prior to pooling were slightly higher than the first generation protease inhibitors, between 50%-89% [110-113, 115-118, 301, 308, 312]. The range of effectiveness rates was similar and between 48%-80% [289, 316, 319, 332, 336, 344]. No observational studies for DCV/PR were identified in the systematic review. Following pooling, the SVR rate in SMV/PR RCTs was 65% compared to 53% in the observational studies (p<0.171). This represented an absolute difference of 12%. In SOF/PR studies, the pooled SVR rates were 89% and 69% in the clinical trials and observational studies, respectively (p<0.0001), an absolute difference of 20%.

4.4.2.2 Interferon-free Regimens

For SOF+RBV, a DAA in combination with RBV, the SVR rates in RCTs ranged from 50%-77% prior to pooling and the effectiveness rates also ranged from 50%-77% [121,

[307, 314] in observational studies. The pooled efficacy rate was 64% with an effectiveness rate of 63%.

In the DAA dual combinations with or without ribavirin (SOF/SMV±RBV, 3D±RBV, SOF/DCV±RBV and SOF/LDV±RBV), the efficacy rates and effectiveness rates were higher than those observed for the IFN-based regimens. In RCTs, the efficacy rates ranged from 84%-99% across the 19 studies and effectiveness rates ranged from 72%-100% across the 20 studies [123-130, 289, 298, 299, 302-306, 309-311, 313, 316, 319, 320, 325, 326, 329-332, 337, 341, 344-346, 349, 350, 352, 354]. Following pooling, the SVR rate in SOF/SMV±RBV RCTs was 89% compared to 80% in the observational studies (p<0.0001). This represented an absolute difference of 9%. In 3D±RBV studies, the pooled SVR rates were 96% and 95% in the clinical trials and observational studies, respectively (p<0.0001), representing an absolute difference of 1%. For SOF/DCV±RBV and SOF/LDV±RBV RCTs, the pooled SVR rates were 98% and 97%, respectively, compared to 93% (p=0.26) and 94% (p<0.0001) for the observational studies. Correspondingly, these represented absolute differences of 5% and 3%.

Table 9: Pooled SVR rates for the clinical trials and observational studies

Treatment Regimen	Study Type	n	SVR12/24 (%)	*p-value*
TPV/PR	Clinical trials	1813	71	<0.0001*
	Observational studies	7309	60	
BOC/PR	Clinical trials	1397	64	<0.0001*
	Observational studies	7916	52	
SMV/PR	Clinical trials	1515	65	0.171
	Observational studies	32	53	
DCV/PR	Clinical trials	12	83	-
	Observational studies	-	-	
SOF/PR	Clinical trials	500	89	<0.0001*
	Observational studies	1717	69	
SOF+RBV	Clinical trials	97	64	0.85
	Observational studies	72	63	
SOF/SMV±RBV	Clinical trials	580	89	<0.0001*
	Observational studies	3571	80	
3D±RBV	Clinical trials	2598	96	0.638
	Observational studies	102	95	
SOF/DCV±RBV	Clinical trials	152	98	0.026*
	Observational studies	243	93	
SOF/LDV±RBV	Clinical trials	2106	97	<0.0001*
	Observational studies	5976	94	

*Statistically significant

Plotting the SVR rate for each regimen against the date on which the drug received EMA marketing authorisation demonstrated the improvement in SVR rate over time, particularly with the introduction of the IFN-free regimens (Figure 18).

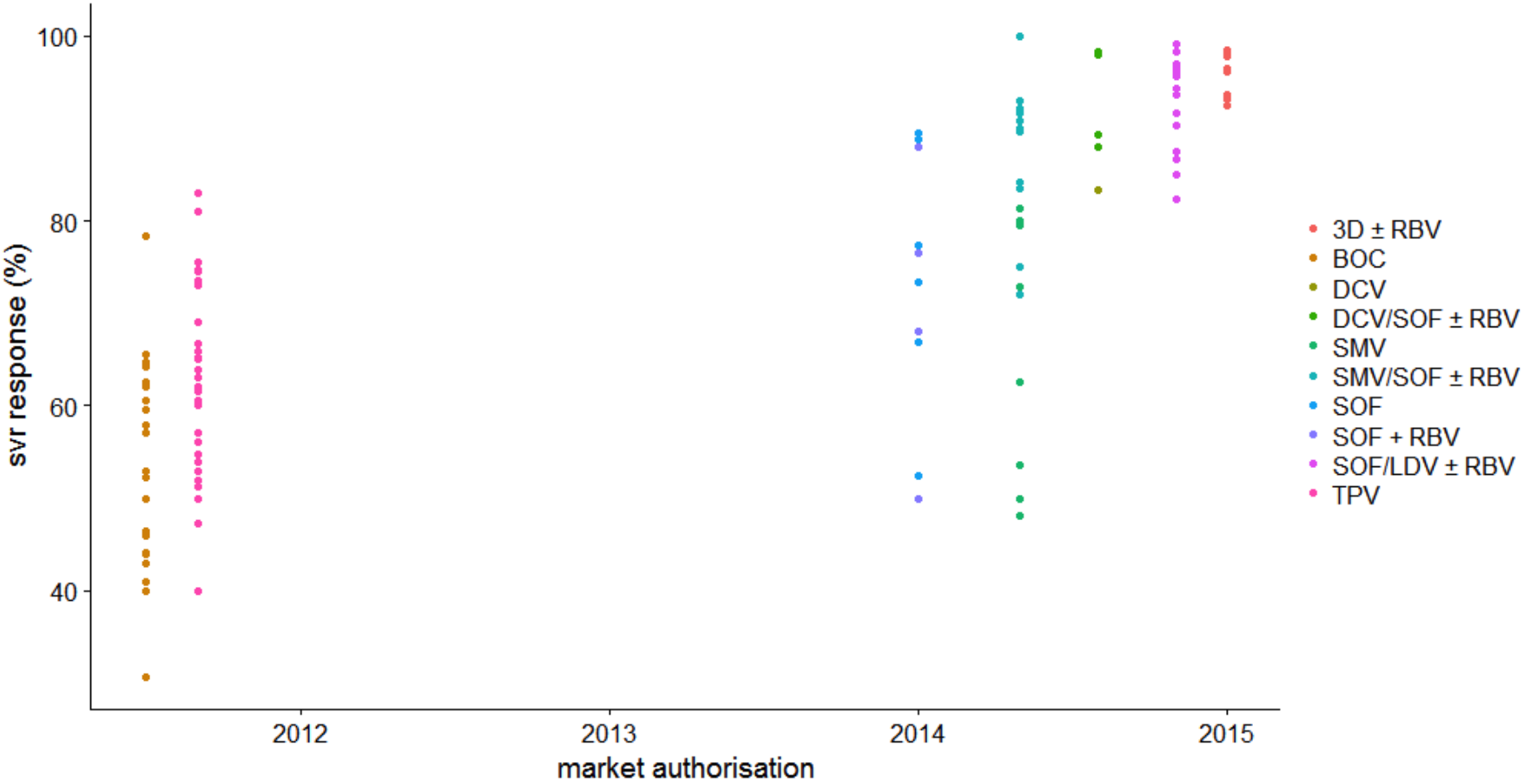


Figure 18: Plot of the pooled SVR rates against the date of EMA marketing authorisation

BOC = BOC/PR, DCV = DCV/PR, SMV = SMV/PR, SOF = SOF/PR, TPV = TPV/PR

4.4.3 Quality Assessment

4.4.3.1 Clinical Trials

The risk of bias graph and the risk of bias summary assessing the quality of the forty-three clinical trials are presented in Figure 19 and Figure 20. Following the assessment of quality, a high risk of bias was considered to be present in 2%, 16%, 42% and 28% of the random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessment domains, respectively. The remaining domains, incomplete outcome data, selective reporting and other bias, were considered to be at low risk of bias.

4.4.3.2 Observational Studies

The quality of observational studies using the NOS is presented in Figure 21. The mean NOS score of the 43 included studies was 6, with a range from 5-8. Six studies had a rating of 8 stars, 2 studies had a rating of 7 stars, 24 had a rating of 6 stars and 11 had a 5 star rating. Risk of bias was greatest in the comparability domain with 81% considered at high risk of bias for confounding. Eight studies were awarded two stars indicating that these studies were adjusted for potential confounding factors. The remainder of the studies failed to score any stars for this domain. Studies that did not undertake appropriate statistical analysis such as multivariate logistic regression or propensity scoring were at risk of confounding by indication. The risk of bias at the outcome level for 43 observational studies is summarized in Appendix 1 Table A 3.

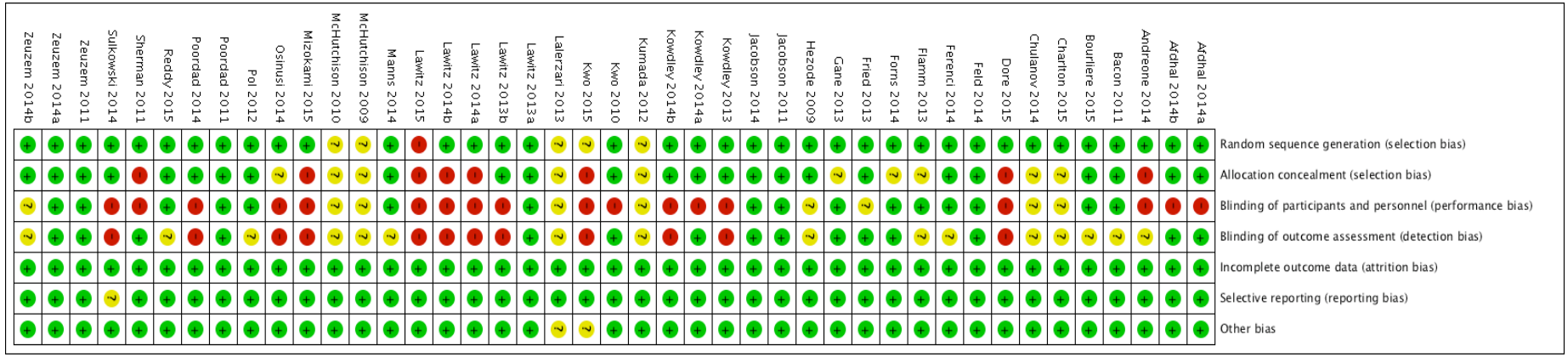


Figure 19: Risk of bias summary
Review authors' judgements about each risk of bias item for each included study.

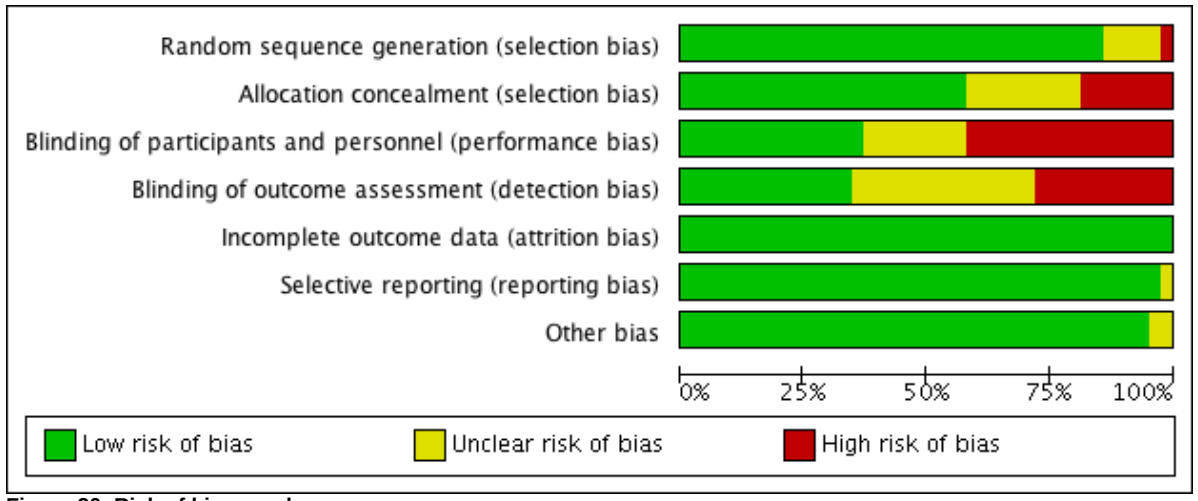


Figure 20: Risk of bias graph
Review author's judgements on each risk of bias domain presented as percentages across all included studies

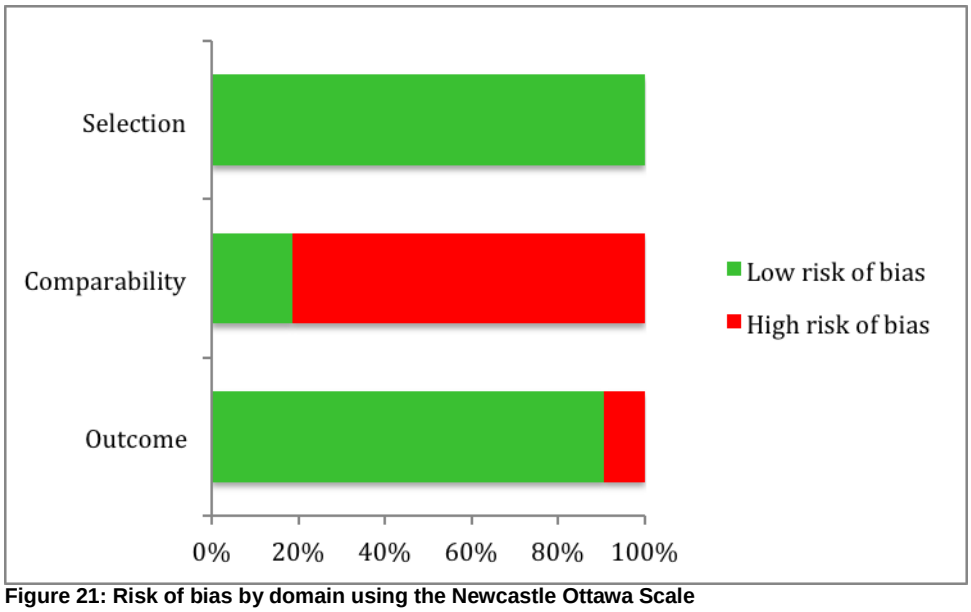


Figure 21: Risk of bias by domain using the Newcastle Ottawa Scale
The green bar represents the percentage of studies with a low risk of bias over the number of studies assessed.

4.4.4 Sensitivity Analysis

In order to investigate the possible impact of bias on outcomes, all studies, both clinical trials and observational studies, identified as being associated with a high risk of bias (any red in Figure 19) and those with significant uncertainty around their risk of bias (≥ four yellow in Figure 19) were excluded and the outcome analysis was repeated (Table 10). Pooled SVR rates are presented in the Appendix 1 Table A 4. Following the exclusion of clinical trials and observational studies associated with a high risk and unclear levels of bias, no clinical trials remained that reported SVR rates for SMV/PR, DCV/PR, SOF/SMV±RBV and SOF/DCV±RBV. Similarly, when observational studies associated with a high risk of bias (NOS score ≤ 6) were excluded, no observational studies remained that reported SVR rates for SOF/PR, SOF+RBV and SOF/DCV±RBV.

Table 10: Studies excluded from the sensitivity analysis

Study	Risk of Bias (Comment)
Afdhal 2014a	High (Performance bias)
Afdhal 2014b	High (Performance bias)
Andreone 2014	High (Selection and Performance bias)
Dore 2015	High (Selection, Performance and Detection bias)
Kowdley 2013	High (Performance and Detection bias)
Kowdley 2014a	High (Performance Bias)
Kowdley 2014b	High (Performance and Detection bias)
Kwo 2010	High (Performance bias)
Kwo 2015	High (Selection, Performance and Detection bias)
Lawitz 2013b	High (Performance and Detection bias)
Lawitz 2014a	High (Selection, Performance and Detection bias)
Lawitz 2014b	High (Selection, Performance and Detection bias)
Lawitz 2015	High (Selection, Performance and Detection bias)
Mizokami 2015	High (Selection, Performance and Detection bias)
Osinusi 2014	High (Performance and Detection bias)
Poordad 2014	High (Performance and Detection bias)
Sherman 2011	High (Selection bias)
Sulkowski 2014	High (Performance and Detection bias)
Kumada 2012	Significant uncertainty (Selection, Performance and Detection bias – not reported in studies)
Lalezari 2013	Significant uncertainty (Selection, Performance and Detection bias – not reported in studies)
McHutchison 2009	Significant uncertainty (Selection, Performance and Detection bias – not reported in studies)
McHutchison 2010	Significant uncertainty (Selection, Performance and Detection bias – not reported in studies)

Analysis of the pooled SVR rates after excluding studies at high risk (and unclear risk) of bias resulted in some changes to the SVR rates. In the clinical trials, the pooled SVR rates fell by 0.2%-4.4% for all regimens, with the exception of SOF+RBV, which increased by 12%. The greatest reduction in SVR rate (-4.4%) occurred in the pooled analysis of SOF/LDV±RBV clinical studies. In the observational studies, pooled SVR rates for TPV/PR, BOC/PR and SMV/PR fell by 2.8%, 0.2% and 5%, respectively. There was no change in the SVR rate for 3D±RBV studies while the pooled SVR rate for SOF/LDV±RBV and SOF/SMV±RBV increased by 0.2% and 4.6%, respectively, when high risk studies were excluded.

4.5 Discussion

The HCV treatment landscape has evolved rapidly in the last number of years and has led to significantly improved SVR rates. This breakthrough began with the advent of the first-generation DAAs, TPV/PR and BOC/PR, and were followed by second-generation protease inhibitors, SMV/PR, DCV/PR and SOF/PR. Despite the improvement in SVR rates, patients treated with IFN-based regimens were burdened with significant side effects and complex treatment regimens. The ability of IFN-free therapies to dramatically improve virological clearance heralded a new era in clinical therapeutics, as the prospect of cure for a chronic viral infection becomes a reality [356].

This study demonstrated the variation in outcomes that can be observed between clinical trials and observational comparative effectiveness studies. Ten DAA-based therapeutic combinations now available for the treatment of GT1 HCV-infected patients were identified. The improvement in SVR rates that came with advances in the development of therapies that targeted more specific and distinct sites in the HCV replication process were highlighted and we report that the interferon-free, DAA dual

combinations (SMV/SOF±RBV, 3D±RBV, SOF/DCV±RBV and SOF/LDV±RBV) are the most effective regimens for the treatment of HCV GT1 infection.

Further investigation into the variation of SVR rates highlighted the disparity in baseline demographics and HCV characteristics of the populations included in RCTs as compared with those included in observational studies. Statistically significant differences were found between the RCT and observational study populations. In the studies that included IFN-based regimens, the observational studies had a consistently greater proportion of males, but more significantly, a greater proportion of patients with previous treatment experience and cirrhosis. Similarly, in the studies of IFN-free regimens, the observational studies commonly included a higher proportion of patients with cirrhosis but the proportion of patients with previous treatment experience was frequently lower in the observational studies.

The absolute difference in pooled SVR rates between RCTs and observational studies was significant for some regimens. It is possible that the disparity in population demographics may account for the differences between the efficacy and effectiveness rates observed. Analysis of the demographic data from RCTs that studied the efficacy of IFN-based regimens showed favourable SVR rates in patients who were treatment naïve and non-cirrhotic. However, in the real world setting, the patient population is more diverse. With a greater proportion of patients considered difficult-to-treat, the effectiveness rate in the real world clinical setting was 11%-20% lower than those observed in RCTs. A lack of specific subpopulation data (i.e. SVR rates in patients with cirrhosis or those with previous treatment experience) prevented the direct comparisons of efficacy and effectiveness rates between these patient subgroups. Therefore, it is difficult to determine the true differences in SVR rates in patients with cirrhosis (particularly in advanced cirrhosis) between RCT and observational studies.

However, we can hypothesise that the higher proportion of patients with cirrhosis in the observational studies may have contributed to the lower rates of effectiveness.

In the interferon-free, DAA dual combination (SMV/SOF±RBV, 3D±RBV, SOF/DCV±RBV and SOF/LDV±RBV) regimens, the gap between efficacy and effectiveness rates narrowed, and in some cases, rates were almost identical, in particular for the 3D±RBV regimen. Nonetheless, disparities in the baseline characteristics between the populations were still apparent. Patients with cirrhosis continued to be under-represented in RCTs but these dual combinations have demonstrated similarly high efficacy rates in both patients with and without cirrhosis.

The quality assessment tools, Cochrane's Risk of Bias and the NOS allowed us to assess whether the quality of the study had an impact on the outcomes obtained. Our sensitivity analysis in which we re-analysed the data following the exclusion of studies considered at high risk of bias (and those with significant uncertainty around the risk of bias), indicated that SVR rates did not differ substantially when studies considered at low risk of bias were analysed alone, with the exception of one regimen SOF+RBV, where the exclusion of one study by Lalezari *et al* resulted in a +12% difference in the SVR rate [307]. Despite this, there continues to be a requirement to utilise methods to address confounding in observational studies, such as multivariate logistic regression and propensity scoring. While observational studies may be more reflective of the real world populations, it is crucial that the studies are well-designed and the highest quality of evidence is produced. It is now more important than ever that decision-makers consider the evidence from observational studies, in addition to the RCT evidence, and the quality of this evidence, to inform or revise policies and decisions about coverage and reimbursement of high cost treatments.

Given that the goal of the BTD program is to identify promising drug candidates early in the clinical development timeline, expedite the development and review process via intensive guidance from the FDA and the EMA and provide patients with access to approved therapies as quickly as possible, non-comparative data are often considered sufficient for providing evidence of early clinical benefit [357]. These clinical trials include limited numbers of carefully selected patients. Thus, it is not uncommon for selected patient subgroups, such as those with decompensated cirrhosis, renal failure or other comorbidities to be excluded from these studies [358]. These are often the most complex and difficult-to-treat patients in clinical practice, and a marketing authorisation can be granted without any evidence from these subgroups. Therefore, this study demonstrates the importance of including a patient population in RCTs that closely mimics the patient population in real world clinical practice with particular emphasis on the inclusion of difficult-to-treat patients. This allows for meaningful determinations to be made about probable effectiveness rates in clinical practice.

From the perspective of the regulator (such as the FDA and EMA), observational studies can play an important role in the post-marketing surveillance and generation of evidence for these difficult-to-treat patient groups. If the inclusion of such patients in RCTs was not possible or unethical, the requirement for thorough, and early, post-marketing surveillance, would enable the effectiveness of the regimen to be established at an early stage following authorisation.

There were several limitations to this study. It is possible that the systematic review was subject to publication bias. Publication bias occurs when studies of statistically significant or clinically favourable results are more likely to be published than studies

with non-significant or unfavourable results. While all resources and search strategies were used to ensure all relevant studies were included, it is possible that trial sponsors failed to make results of unfavourable trials available and thus, the potential for publication bias must be considered. Additionally, pooling data from studies with heterogeneous design requires awareness of the potential to introduce bias. Pooling, as undertaken above, is the simplest and most naively intuitive way of summarising the information from several clinical trials. However, this approach does not consider the validity of the comparisons, assumes all trial designs are the same and therefore, is often subject to bias [359].

4.6 Conclusion

Recent therapeutic advances are transforming the HCV landscape and there is now an unprecedented prospect of cure for this chronic viral infection with the possibility of global eradication of the disease (subject to fiscal restraints). While demonstrating the superiority of DAA dual combination interferon-free treatment combinations above those that contain the PR backbone, this study highlights the need for clinical trials to include a patient population that is more representative of those awaiting treatment in the clinical setting.

This study provides evidence that the populations included in clinical trials tend not to reflect the population treated in the clinical setting and as a result, the efficacy rates often differ from the effectiveness rates reported in the real world. Clinical trials commonly exclude difficult-to-treat patients, those with the most severe presentation of a disease (e.g. decompensated cirrhosis) and/or those with co-morbid conditions (e.g. HIV-co-infection or renal insufficiency). While appropriate eligibility criteria are essential for the internal validity of the RCTs, it often results in the selection of an ‘ideal’ patient

population most likely to demonstrate the efficacy and safety outcomes required to ensure regulatory approval.

Historically, RCT evidence has been considered the gold standard in the hierarchy of evidence for evaluating the efficacy and safety of interventions. The BTD aims to fast-track the approval of marketing authorisations for promising drugs, potentially relying exclusively on well-controlled, non-randomised studies as appropriate evidence of efficacy for regulators. Thus, not only does the clinical trial population poorly reflect the clinical setting but we also consider whether the BTD compromises the scientific strength of the clinical trial evidence at the top of the evidence hierarchy. Without the requirement for randomisation, blinding and concealment, the design of these studies and thus, the quality of evidence for BTD designated treatments do not differ significantly from the design of observational studies. Licensing of treatments for HCV infection in recent years is a testament to this phenomenon whereby many agents and treatment regimens were licensed based on non-comparative, single arm studies driven by the desire to bring treatments to the market as quickly as possible. This has also occurred in a number of other therapeutic areas. Therefore, as observational studies may be more reflective of the real world populations and the quality of the evidence may not differ significantly from that of some clinical trials, it is now more important than ever that decision-makers consider the evidence from observational studies accrued prospectively in the post-HTA era, in addition to the RCT evidence, and the quality of this evidence, to inform or revise policies and decisions about coverage and reimbursement.

Additionally, in instances where it is unethical or impossible to include a patient population representative of clinical practice in the RCTs, a regulatory requirement for observational studies may assist in the generation of further evidence for these patient

groups and to allow for continued monitoring and analysis of outcomes, identifying adverse events or unwanted outcomes that did not appear during the drug approval process.

Chapter 5

Chapter 5 Generation and Analysis of Observational Data from the National HCV Treatment Registry

This chapter is composed of three separate sub-studies. Sub-study 1 reports the effectiveness of the protease inhibitors, telaprevir, boceprevir and simeprevir, in combination with pegylated-interferon and ribavirin in a cohort of HCV-infected patients with or without cirrhosis. Sub-study 2 reports the effectiveness of the interferon-free regimen, sofosbuvir/ledipasvir with or without ribavirin in a cohort of patients with advanced liver disease and/or decompensated cirrhosis who received treatment under the Irish early access programme. Sub-study 3 reports the effectiveness of interferon-free regimens in a cohort of patients with compensated cirrhosis. These patients had been prioritised to receive treatment after all those with advanced liver disease and/or decompensated cirrhosis had been treated.

5.1 Introduction

The value of including outcomes from clinical trials for estimating treatment effect is limited by strict inclusion and exclusion criteria in the trials, with results which may have limited applicability to patients in real world clinical settings [11-13, 163, 164]. The approval of first-generation protease inhibitors for use in combination with PR for the treatment of HCV infection marked the beginning of the recent evolution in the HCV treatment landscape. This also led to the establishment of ICORN and the development of the Irish national HCV treatment registry. The initial research undertaken for this thesis utilises data within the national HCV treatment registry and aims to establish the effectiveness of the new treatments for HCV infection in the Irish clinical setting. Both the baseline demographic and HCV characteristic profile of these patients and the outcomes from the treatment will be valuable for HTA agencies and decision-makers in the post-reimbursement era.

5.2 Methods

The Irish national HCV treatment registry utilises a prospective, longitudinal, observational methodology. Since 2012, patients prescribed HCV DAA treatment have been enrolled for participation in the registry. Data on treated patients were collected through chart review and interrogation of electronic patient records (EPR), and subsequently entered into the web-based registry.

The candidate periodically visited the treatment sites and manually abstracted data through chart review and interrogation of electronic patient records (EPR) to facilitate collation. Site visits are facilitated through arrangements with nursing staff at each site. Data was captured on data collection sheets that mirrored the registry data inputs. For two treatment sites, data was collected on site by the nursing staff and sent to the candidate. Demographic and clinical data were collected at baseline, throughout treatment and in the post-treatment follow-up period. Manual data collected, for each patient, at site visits was entered into the registry in preparation for retrieval and analysis.

Treatment effectiveness was measured as the SVR12 (for the IFN-free regimens) or SVR24 (for the IFN-based regimens) following treatment completion. Where a SVR12 or SVR24 was not achieved, the frequency of virological failure and relapse were recorded. Additionally, patients who were lost-to-follow up or had discontinued treatment prematurely as a result of AEs, non-compliance, death or other factors were captured.

For all patients, the decision to initiate treatment and the selection of the treatment regimen was at the discretion of the physician.

5.2.1 Sub-study 1 – Effectiveness of Interferon-based Therapy in HCV-Infected Patients

For this study, we analysed the data for 338 patients who underwent treatment with IFN-based regimens for HCV GT1 infection between June 2012 and December 2014. Patients were eligible if they were HCV GT1 infected and 18 years or older. Cirrhotic and non-cirrhotic patients and HIV co-infected patients were eligible for inclusion. Patients were treated with either:

- Telaprevir 1125mg taken twice daily in combination with PR for 12 weeks followed by 12- or 24-weeks of PR alone (TPV/PR).
- A lead-in of PR for 4-weeks followed by boceprevir 800mg taken three times daily in combination with PR for 24-, 32- or 44-weeks (BOC/PR).
- Simeprevir 150mg taken once daily in combination with PR for 24 or 48 weeks (SMV/PR).

Duration of treatment was determined by baseline patient characteristics and/or in accordance with recommended stopping rules [6, 276].

5.2.2 Sub-study 2 – Effectiveness of Interferon-free Therapy in HCV-Infected Patients with Advanced Liver Disease and/or Decompensated Cirrhosis

For this study, data from 101 patients treated with the IFN-free regimen SOF/LDV±RBV between December 2014 and June 2015 under the EAP were analysed. Eligible patients were those at significant risk of death or irreversible damage from HCV infection within 12 months, irrespective of genotype. Criteria for inclusion were decompensated cirrhosis (ascites, variceal bleed or hepatic encephalopathy (past or current)) or Child Pugh score ≥ 7. HIV co-infected patients were eligible for inclusion.

Patients were treated with:

- Sofosbuvir/ledipasvir (400mg/90mg) taken once daily by mouth with or without weight-based RBV administered orally in two divided doses for 12-weeks (SOF/LDV±RBV).

5.2.3 Sub-study 3 – Effectiveness of Interferon-free Therapy in HCV-Infected Patients with Compensated Cirrhosis

For this study, data for 205 patients treated with the IFN-free regimens from April 2015 to July 2016 were analysed. Patients were eligible for this study if they were treated for HCV infection with an IFN-free regimen, were 18 years or older, and had evidence of compensated cirrhosis (CTP A). HIV co-infected patients were also eligible for inclusion. Based on the 2015 AASLD and EASL guidelines [7, 122], patients were initiated on treatment with one of the following three regimens:

- Sofosbuvir/ledipasvir (400mg/90mg) taken once daily by mouth with or without weight-based RBV administered orally in two divided doses for 12-weeks (SOF/LDV±RBV).
- A combination of 12.5mg ombitasvir, 75mg paritaprevir and 50mg of ritonavir once daily with 250mg dasabuvir with or without weight-based RBV administered orally in two divided doses for 12 weeks, with the exception of those with GT1a, who required 24 weeks of therapy (3D±RBV).
- Sofosbuvir/daclatasvir (400mg/60mg) taken once daily by mouth with or without weight-based RBV administered orally in two divided doses for 24 weeks (SOF/DCV±RBV) [122].

5.3 Statistical Analysis

Descriptive statistics were used to present the baseline characteristics and unadjusted outcomes for the study population. Categorical variables were reported as frequencies

and percentages. Baseline continuous data were expressed as medians (with the interquartile range (IQR)). Univariate analyses were performed using the Chi-square, Fisher's Exact or Student's *t*-test as appropriate. A one-way ANOVA was used to test for significant differences for those elements with greater than two categories. A *p*-value <0.05 was considered significant. Odds ratios were reported with their 95% confidence interval.

Where required, multiple imputation was used to impute missing values on baseline variables that were identified as covariates in the confounding analysis. Despite manually collecting data from the majority of treatment sites, there was still missing data on simple variables such as gender. This arose from the sites, which submitted their data to us, whereby data collection forms were received with incomplete data for these simple variables.

A confounder is a variable that can influence both the treatment assignment and the treatment outcome. The confounding variables were identified through careful analysis of published literature and following consultation with clinical experts. The goal of the multiple imputation was to ensure that there was no missing data for the identified confounding variables. This ensured that we could include all subjects in the PS analysis. Missing data relating to the confounders would have resulted in the exclusion of these subjects before commencing the PS analysis, compromising the outcomes in a dataset already limited by a small sample size. The standard SPSS procedure for multiple imputation using the fully conditional specification statement and the Markov Chain Monte Carlo (MCMC) methodology was used. Imputation was based on a linear regression model.

Propensity scoring was used in both sub-study 1 and sub-study 3†. In sub-study 1, the PS, the probability of being treated with TPV/PR as opposed to BOC/PR, given other known baseline demographics and HCV characteristics, was computed using multivariate logistic regression. Following a review of the literature and consultation with clinicians, nine covariates were entered into the model: previous treatment experience, presence of cirrhosis, age, BMI, GT1, GT1b, IL28B CT, IL28B TT and baseline HCV > 800,000 IU/ml [218-222]. For genotype and IL28B allele, both of which had more than two distinct categories (i.e. GT1 (no subtype), GT1a, GT1b), dummy variables had to be created to represent these subgroups in the regression analysis (Appendix 2 Table A 5 and Table A 6). The resultant PS (range = 0.0 – 1.0) was a single score per patient, with a high score representing a high probability that the patient would be treated with TPV/PR, based on the given information. Prior to applying PS matching, a comparison of confounders between the TPV/PR and BOC/PR groups was completed. The standardised difference was used to compare the mean of continuous and binary variables between treatment groups and was not influenced by the sample size. Three approaches to matching without replacement were employed to match patients who received TPV/PR with patients who received BOC/PR. A treated subject (TPV/PR) was first selected at random. The untreated subject (BOC/PR) whose propensity score was closest to that of this randomly selected treated subject was chosen for matching. This process was then repeated until all untreated subjects had been matched to all treated subjects. In our first approach, naïve matching was used whereby all ninety-four BOC/PR subjects were matched to a TPV/PR subject. A second matching approach was completed where patients were matched on the logit of the PS using a caliper width limit equal to 0.1 of the logit of the propensity score (i.e. the difference of the logit of the PS between the TPV/PR and BOC/PR matched subjects was less than 0.1). Finally, in the third scenario, the caliper width limit was

† Propensity scoring was not used in sub-study 2 because only one treatment regimen, SOF/LDV±RBV was included in the analysis.

extended to 0.2 of the logit of the PS. In all three approaches, each TPV/PR treated subject was matched to the BOC/PR subject with the closest PS. To assess the balance of covariates after PS matching, the balance in measured confounders between treated and untreated subjects within the PS matched sample were compared for all three approaches using standardised differences. Adjusted SVR rates, odds ratios, *p*-values and 95% confidence intervals were calculated.

In sub-study 3, PS stratification was employed as it allowed all the data to be used in a dataset that already contained limited numbers. This tool was applied in the GT1 cohort of patients to determine the adjusted odds ratio of achieving a SVR in those treated with SOF/LDV±RBV compared with 3D±RBV. PS could not be used in other genotypes or treatment regimens due to insufficient patient numbers and a lack of a suitable comparator. The PS, the probability of being treated with SOF/LDV±RBV, as opposed to 3D±RBV, given other known baseline demographics and HCV characteristics, was computed for each individual using a multivariable logistic regression model. Seven covariates were identified after reviewing the literature and consulting with clinicians [121, 360]. Those covariates identified and entered into the model were previous protease-inhibitor treatment failure, previous PR treatment failure, age, gender, GT1a, GT1b, and baseline HCV > 800,000 IU/ml. In this sub-study, we stratified on the propensity score. Subjects were ranked according to the calculated PS and divided into five strata, which were created based on the quintiles of the PS distribution in the cohort. To assess the balance in measured confounders after stratifying on the PS, within-strata standardised differences were computed to compare the distribution of baseline covariates between treated and untreated subjects within the same PS stratum. The mean standardised difference was then determined across the strata. The OR was calculated to express the chances of a SVR12 with 3D±RBV compared with SOF/LDV±RBV.

Demographic and outcome analyses and multiple imputation were conducted using IBM SPSS Version 21 (IBM Corp, Armonk, NY, USA). Propensity scoring was conducted with STATA Version 14 (STATACorp, College Station, Texas, USA).

For all three sub-studies, the effectiveness rates reported in this chapter were compared with efficacy rates reported in pivotal clinical trials and effectiveness rates reported in international real world studies.

5.4 Results - Sub-study 1

A total of 338 patients with HCV infection initiated treatment with TPV/PR (n=215), BOC/PR (n=94) or SMV/PR (n=29). All had reached SVR24 or discontinued treatment prematurely. The majority of patients were male (74%) with a median age of 45 years (IQR 38-54 years). Patients who previously failed to respond to treatment with PR accounted for 29% of the cohort while cirrhosis was present in 27%. HIV co-infection accounted for 7%. IL28B CT was the dominant allele (54%). The proportion of patients with GT1a, 1b and 1 (no subtype) was 54%, 26% and 19% respectively. Two patients treated with SMV/PR were GT4. Baseline HCV-RNA was greater than 800,000 IU/ml in 54% of the cohort (Table 11).

Table 11: Baseline demographics for patients treated with the IFN-based regimens

	Total Cohort*	TPV/PR*	BOC/PR*	SMV/PR*
	n=338	n=215	n=94	n=29
Age – Years, Median (IQR)	46 (38-54)	45 (38-54)	47 (39-56)	48 (35-53)
BMI – kg/m^2 Median (IQR)	26.1 (23.5-28.7)	26.3 (23.9-28.5)	25.9 (21.4-30.6)	26.2 (22.9-28)
Male, n (%)	229/309 (74.1%)	149/202 (73.8%)	63/88 (71.6%)	17/19 (%)
History of cirrhosis, n (%)	82/308 (26.6%)	55/198 (27.8%)	24/93 (25.8%)	3/17 (%)
Treatment Experienced, n (%)	93/325 (28.6%)	66/212 (31.1%)	23/94 (24.5%)	4/19 (%)
HIV co-infected, n (%)	23/313 (7.3%)	23/198 (11.6%)	-	Not available
Haemophilia, n (%)	18/300 (6%)	16/191 (8.4%)	2/94 (2.1%)	Not available
Post liver transplant, n (%)	5/300 (1.7%)	1/191 (0.5%)	4/94 (4.3%)	Not available
Presence of diabetes, n (%)	12/286 (4.2%)	4/187 (2.1%)	8/90 (8.9%)	Not available
IL28B Allele, n (%)				
CC	92/269 (34.2%)	59/179 (33%)	31/86 (36%)	Insufficient data
CT	144/269 (53.5%)	96/179 (53.6%)	47/86 (54.7%)	Insufficient data
TT	33/269 (12.3%)	24/179 (13.4%)	8/86 (9.3%)	Insufficient data
Genotype, n (%)				
G1a	183/338 (54.1%)	119/215 (55.3%)	53/94 (56.4%)	11/29 (37.9%)
G1b	89/338 (26.3%)	55/215 (25.6%)	31/94 (33%)	3/29 (10.3%)
G1 – unspecified	64/338 (19%)	41/215 (19.1%)	10/94 (10.6%)	13/29 (44.9%)
G4	2/338 (0.6%)	-	-	2/29 (6.9%)
Acquisition Risk Factor				
IVDU	138/338 (40.8%)	89/215 (41.4%)	44/94 (46.8%)	5/22 (17.2%)
Anti-D	28/338 (8.3%)	18/215 (8.4%)	10/94 (10.6%)	-
Blood product	36/338 (10.7%)	31/215 (14.4%)	5/94 (5.3%)	-
Other	15/338 (4.5%)	11/215 (5.1%)	4/94 (4.4%)	-
Unknown/not reported	121/338 (35.7%)	66/215 (30.7%)	31/94 (32.9%)	17/22 (82.8%)
Baseline HCV-RNA >800,000IU/ml	161/299 (53.8%)	98/196 (50%)	55/90 (61.1%)	8/13 (61.5%)

BMI = body mass index, IVDU = injecting drug user
*Missing data are a common problem with observational data. Percentages are calculated based on the proportion of available data

5.4.1 Effectiveness

Outcomes for all 338 patients are presented in Figure 22. Overall, 71% (n=240/338) of the cohort completed therapy, with the remaining 29% (n=98/338) discontinuing early due to AEs, virological failure, poor tolerability, non-compliance or for an undetermined reason. The overall rate of SVR24 (unadjusted) was 68% (n=228/338). This included fifteen patients who discontinued prematurely as a result of an AE or non-compliance but achieved a SVR24. Nineteen patients (6%) completed a full course of treatment but relapsed within 24-weeks of completing therapy. There were eight patients (2%) considered lost to follow-up. These patients completed a full course of therapy but failed to return to the clinic for any SVR24 assessment (Figure 22).

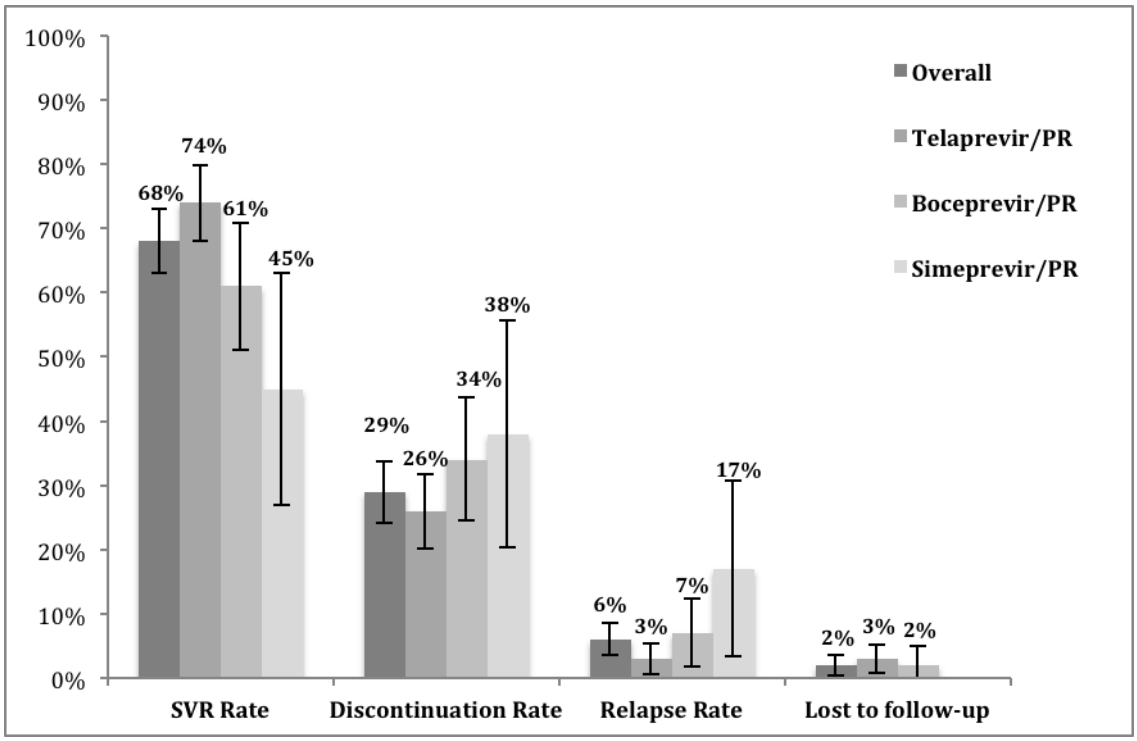


Figure 22: Unadjusted treatment outcomes for the overall cohort and stratified per treatment regimen
Fifteen patients discontinued treatment prematurely but achieved a SVR24; eleven patients treated with telaprevir/PR and four patients treated with boceprevir/PR. These patients are included in both the discontinuation and SVR calculations.

5.4.1.1 Telaprevir/PR and Boceprevir/PR

The unadjusted SVR24 rates were 74% (n=158/215) and 61% (n=57/94) for TPV/PR, and BOC/PR, respectively (Figure 22). Discontinuation and relapse rates were higher in the cohort treated with BOC/PR (34% and 7%, respectively). Prior to adjusting for confounding, the crude odds of SVR24 in patients treated with TPV/PR were 80% greater than those treated with BOC/PR (OR = 1.8, 95% CI 1.08-3, p = 0.025).

The unadjusted SVR24 rates varied according to the presence or absence of baseline cirrhosis, prior treatment experience and GT1 subtype (Table 12). In the absence of cirrhosis, the SVR24 was 79% (n=113/143) for patients treated with TPV/PR and 65% (n=45/69) for patients treated with BOC/PR. Presence of cirrhosis led to SVR24 rates of 66% (n=36/55) and 50% (12/24) in TPV/PR and BOC/PR cohorts, respectively.

The SVR24 for treatment naïve patients treated with TPV/PR was 75% (n=109/146) and 57% (n=44/71) for patients who received BOC/PR. Previous treatment experience resulted in SVR24 rates of 73% and 62% in those treated with TPV/PR and BOC/PR respectively. The SVR24 rates were higher in GT1a and GT1b patients treated with TPV/PR compared with those treated with BOC/PR (71% and 84% vs. 59% and 58% for GT1a and GT1b TPV/PR and BOC/PR, respectively).

5.4.1.2 Simeprevir/PR

Given the limited amount of both baseline demographics and outcomes data available for patients treated with SMV/PR, the results obtained should be interpreted with caution given the small sample size and large quantity of missing baseline data. Applicability to the real world may be compromised. Additionally, given the limited number of SMV/PR patients included in the entire cohort, this subgroup was excluded from the PS analysis.

The unadjusted SVR24 in patients treated with SMV/PR was 45% (n=13/29). Discontinuation and relapse rates were higher in the SMV/PR cohort (38% (n=11/29) and 17% (n=5/29), respectively) when compared with TPV/PR and BOC/PR (Figure 22). SVR24 was not achieved in the three patients known to have cirrhosis. In the absence of cirrhosis, the SVR24 was 71% (n=10/14). The SVR24 was higher in the treatment naïve cohort (53%, n=8/15) compared to patients with previous treatment experience (50%, n=2/4). In GT1a patients, the SVR24 was 46% (n=5/11) while none of the three GT1b patients achieved a SVR24.

Table 12: Unadjusted SVR rates among patients stratified by treatment choice and baseline HCV characteristics

	Total* N=338			TPV/PR* N=215			BOC/PR* N=94			SMV/PR* N=29		
	n/N	SVR24 %	95% CI	n/N	SVR24 %	95% CI	n/N	SVR24 %	95% CI	n/N	SVR24 %	95% CI
Overall	228/338	68	62.5-72.5	158/215	74	67.6-79.4	57/94	61	50.7-70.5	13/29	45	26.7-62.9
Absence of cirrhosis	168/226	74	68.6-80	113/143	79	72.3-85.7	45/69	65	54-76.4	10/14	71	47.7-95.1
Presence of cirrhosis	48/82	59	47.8-69.2	36/55	66	52.9-78.1	12/24	50	30-70	0/3	0	-
Treatment naïve	161/232	69	63.5-75.3	109/146	75	67.6-81.8	44/71	57	36.2-76.4	8/15	53	28.1-78.5
Treatment-experienced	63/93	68	58.2-77.2	48/66	73	62-83.4	13/23	62	50.7-73.3	2/4	50	1-99
Genotype 1a	120/183	66	58.7-72.5	84/119	71	62.4-78.8	31/53	59	45.2-71.8	5/11	46	16.1-74.9
Genotype 1b	64/89	72	62.6-81.2	46/55	84	78.8-93.4	18/31	58	40.7-70.5	0/3	0	-
Genotype 1 (no subtype)	44/64	69	57.9-80.9	28/41	68	54.7-83.7	8/10	80	55.2-104.8	8/13	62	35-88

*Missing data are a common problem with observational data. Percentages are calculated based on the proportion of available data

5.4.2 Propensity Score Matched Analysis

Prior to applying PS matching, a comparison of confounders between the TPV/PR and BOC/PR groups was completed. The standardised difference of confounding variables prior to matching is presented in Table 13. Variables with a standardised difference greater than 0.1 exhibited imbalance between the two treatment groups.

Table 13: Standardised difference of confounding variables between TPV/PR and BOC/PR patients prior to matching

	Mean TPV/PR	Mean BOC/PR	Standardised Difference
Treatment-experienced	0.31	0.24	0.154
Presence of cirrhosis	0.29	0.26	0.058
Age	45.73	47.62	-0.174
BMI	26.7	26.73	-0.006
Baseline HCV>800,000IU/ml	0.49	0.6	-0.203
GT1	0.19	0.11	0.225
GT1b	0.26	0.33	-0.153
IL28B CT	0.49	0.53	-0.072
IL28B TT	0.17	0.11	0.119

BMI = body mass index

5.4.2.1 Naïve Matching

After matching, ninety-four matched pairs were formed. The standardised difference of confounding variables after naïve matching showed improvements in the balance between the two groups (Table 14).

The adjusted SVR24 rates were 73% (n=69/94) and 61% (n=57/94) for TPV/PR and BOC/PR, respectively. The adjusted odds of SVR24 in patients treated with TPV/PR were 76% greater than those treated with BOC/PR (OR = 1.76, 95% CI 0.868-3.58, p = 0.116).

5.4.2.2 Matching with a 0.1 Caliper Limit

After matching and applying a caliper width limit of 0.1, ninety matched pairs were formed. Four pairs were excluded after the caliper limit was applied due a difference in

the logit of the PS being greater than 0.1. The confounding variables after matching showed greater balance than prior to matching (Table 14).

The adjusted SVR rates were 73% (n=66/90) and 60% (n=54/90) for TPV/PR and BOC/PR, respectively. The adjusted odds of SVR24 in patients treated with TPV/PR were 87% greater than those treated with BOC/PR (OR = 1.87, 95% CI 0.89-3.95, *p* = 0.097).

5.4.2.3 Matching with a 0.2 Caliper Limit

After increasing the caliper width limit to 0.2, ninety-one matched pairs were formed. Three pairs were excluded after this width limit of 0.2 was applied. After matching, the standardised difference for all covariates was less than 0.1 (Table 14).

The adjusted SVR24 rates were 74% (n=67/91) and 60% (n=57/91) for TPV/PR and BOC/PR, respectively. The adjusted odds of SVR24 in patients treated with TPV/PR were 85% greater than those treated with BOC/PR (OR = 1.85, 95% CI 0.883-3.88, *p* = 0.102).

Table 14: Standardised difference of confounding variables between TPV/PR and BOC/PR after the three approaches to matching

	After naïve matching	After 0.1 caliper limit	After 0.2 caliper limit
Treatment-experienced	0.000	0.04	0.04
Presence of cirrhosis	0.000	0.022	0.022
Age	-0.014	0.011	0.016
BMI	-0.003	-0.005	-0.002
Baseline HCV>800,000IU/ml	0.019	0.019	0.019
GT1	-0.022	0.000	0.000
GT1b	0.019	0.039	0.039
IL28B CT	0.018	-0.018	-0.018
IL28B TT	0.027	0.072	0.028

BMI = body mass index

Figure 23 illustrates the SVR24 rates prior to and after applying the PS matching methodology. There is no significant change in the treatment effect after PS matching.

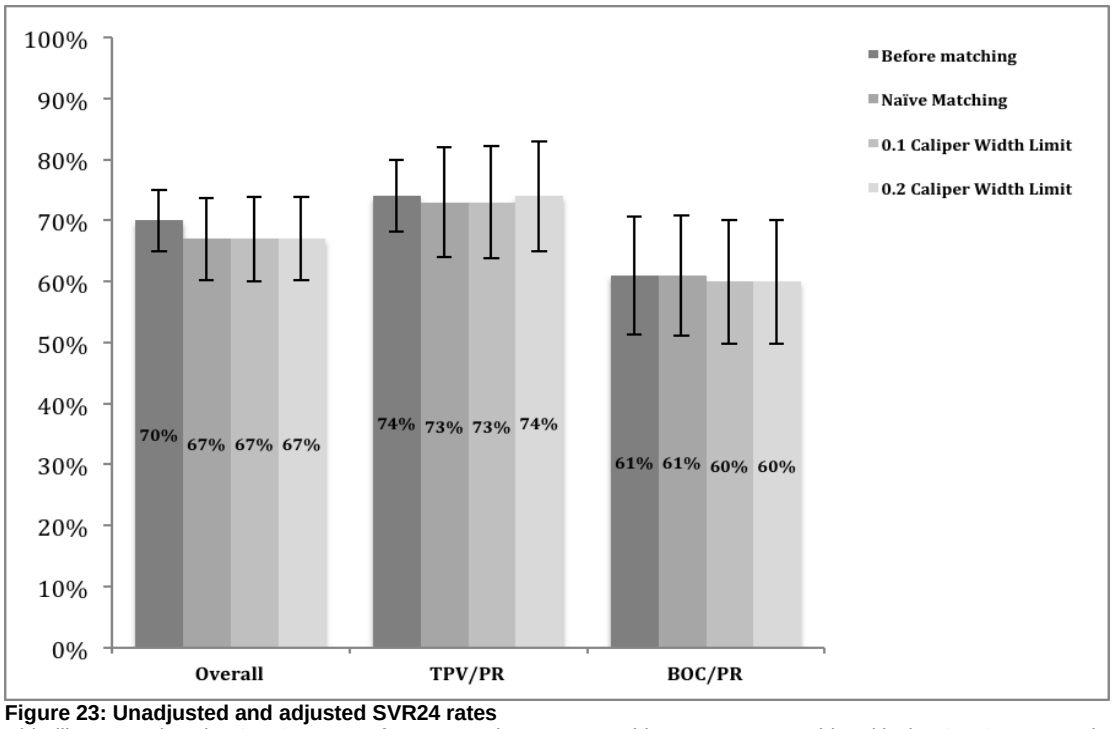


Figure 23: Unadjusted and adjusted SVR24 rates
This illustrates that the SVR24 rates after propensity score matching were comparable with the SVR24 rates prior to matching.

5.4.3 Comparison with Clinical Trial Data

Pivotal TPV/PR and BOC/PR clinical trials were undertaken exclusively in treatment naïve or treatment-experienced patients. Comparison of the adjusted outcomes from this study with clinical trial data demonstrates that the adjusted SVR24 rates in both the TPV/PR and BOC/PR groups are comparable to those obtained in the clinical trials. In the TPV/PR treatment-experienced group, the adjusted SVR24 rates in this study demonstrate an improvement on the SVR24 rates obtained in the trials while the adjusted SVR24 rates for the BOC/PR treatment-experienced are lower in this study when compared with the clinical trial data (Figure 24).

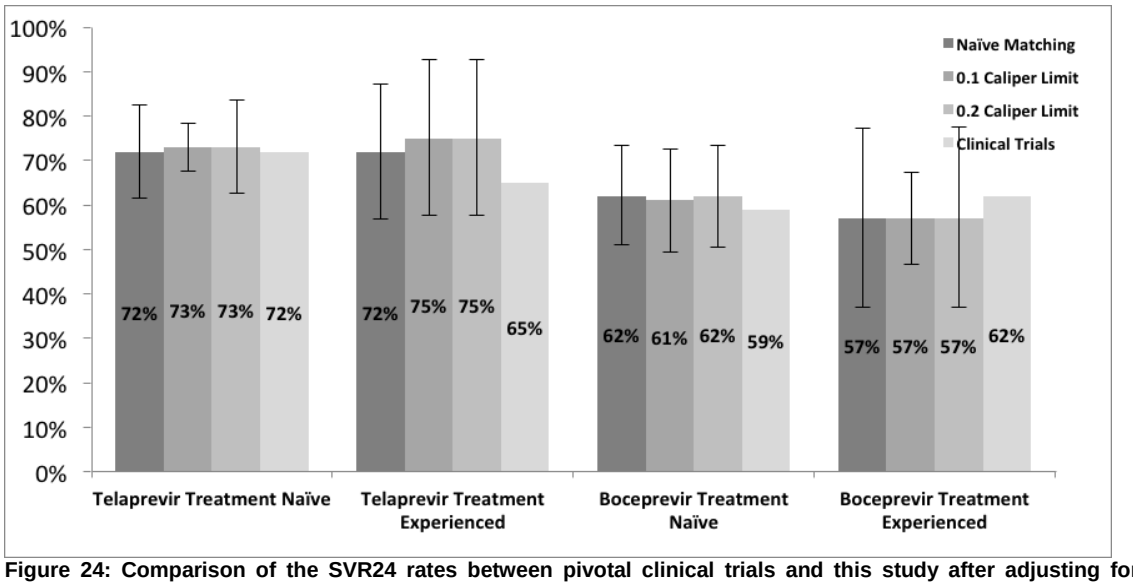


Figure 24: Comparison of the SVR24 rates between pivotal clinical trials and this study after adjusting for confounding.

5.4.4 Comparison with Other International Real World Studies

A number of other real world studies assessing the effectiveness of TPV/PR and BOC/PR were initiated in the USA and Europe. We compared the SVR24 rates from our cohort with outcomes reported in the US-based HCV-TARGET study and the German-based PAN study (Figure 25) [290, 338]. In the TPV/PR cohorts, a statistically significant difference was observed in the SVR24 rates between this study and both the HCV-TARGET and PAN studies (p<0.05). In the BOC/PR cohorts, a statistically significant difference was observed between our study and the HCV-TARGET (p<0.05) study but the difference between our study and the PAN study was not statistically significant (p=0.141).

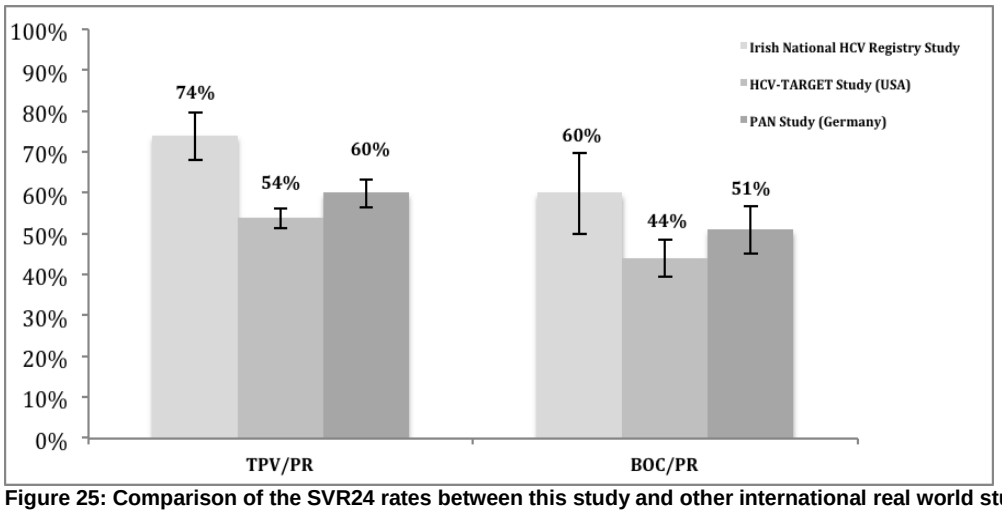


Figure 25: Comparison of the SVR24 rates between this study and other international real world studies

5.5 Discussion – Sub-study 1

For the IFN-based regimens, adjusted SVR24 rates, following PS matching were reported for TPV/PR and BOC/PR. The effectiveness rate in the TPV/PR cohort was superior to the BOC/PR cohort. This was driven by a greater proportion of premature discontinuations in those treated with BOC/PR. We excluded SMV/PR from the PS analysis due to the limited patient numbers and thus, unadjusted SVR24 rates were presented. The outcomes in patients treated with SMV/PR were disappointing, with a SVR24 rate of 45%, in addition to a high discontinuation rate. However, given the limited patient numbers, this data should be interpreted with caution.

After completing the three approaches to PS matching and adjusting for confounding in our data, we conclude that there was no difference in the SVR24 rates of the TPV/PR and BOC/PR groups prior to, and after PS matching (Figure 23). However, the small sample size limits the conclusions that can be made about the effect of PS matching. While *p*-values after matching contrasted with the *p*-value before matching (*p*-values were statistically significant after matching), the wide confidence intervals indicate significant uncertainty surrounding the outcomes. Propensity score adjustment remains

a tool that can be applied to future analysis. However, we suggest, where possible, using a larger sample size in order to reduce the uncertainty around the outcomes.

Comparison of the SVR24 rates in TPV/PR treatment naïve and treatment-experienced subgroups with the ADVANCE and ILLUMINATE treatment naïve and REALIZE treatment-experienced clinical trials indicated that the outcomes for these treatment regimens in the real world clinical setting in Ireland are comparable, or better, than those reported in these trials [97-99]. The adjusted SVR24 rates in our TPV/PR treatment-experienced group were between 7-10% higher than those observed in the REALIZE trial. The adjusted SVR24 rates in our BOC/PR treatment naïve group were comparable with outcomes from the SPRINT-1 and SPRINT-2 clinical trials but the results in the RESPOND trial were approximately 5% greater than the adjusted SVR24 rates in our BOC/PR treatment-experienced group [103, 105].

The SVR outcomes were also compared with other international real world studies. The SVR24 rate from the Irish national HCV registry compared favourably with the outcomes from other international real world studies. Comparing key baseline demographics and HCV characteristics between the three studies demonstrated that our cohort was younger and had a higher proportion of males. However, our Irish cohort did include a lower proportion of patients with previous treatment experience while the proportion of patients with cirrhosis was lower than in the HCV-TARGET study but higher than the proportion in the PAN study [290, 338]. These demographic details suggest that the cohorts in the HCV-TARGET and PAN studies would be considered more difficult-to-treat than the Irish cohort and therefore, is reflected in the lower SVR24 rates reported in these studies.

5.6 Results – Sub-study 2

Between December 2014 and June 2015, 101 patients, treated with SOF/LDV±RBV for 12 weeks under the EAP, completed treatment (to SVR12 or premature discontinuation). Three-quarters were GT1 (74%) and 24% were GT3. The remaining two patients were GT4 and mixed GT. The majority of patients were male (64%) and between the ages of 40 and 64 years (72%) with a median age of 54 years (IQR 47-61). There were fifteen patients with CTP A cirrhosis who were included in the EAP on the basis of previous history of decompensation or were post orthotopic liver transplant. The remaining 85% had a CTP score B or C. Half of the patients had failed to respond to previous HCV treatment; 39% had failed to respond to the dual therapy combination of PR, while 12% had failed to respond to treatment with a first-generation protease inhibitor, TPV/PR, BOC/PR or SMV/PR (Table 15).

Table 15: Baseline demographics of the n=101 patients treated with SOF/LDV±RBV under the EAP

	Total* n=101	Died on Treatment* n=8	Survived treatment* n=93
Median age (IQR), yrs.	54 (47-61)	50 (46-52)	54 (47-62)
18-39, n (%)	10/101 (9.9)	-	10/93 (10.8)
40-64, n (%)	73/101 (72.3)	8/8 (100)	65/93 (69.9)
≥65, n (%)	18/101 (17.8)	-	18/93 (19.4)
Male, n (%)	65/101 (64.4)	5/8 (62.5)	60/93 (64.5)
Median ALT (range), *IU/L*	57 (14-350)	43 (21-64)	57 (14-350)
Median albumin (range), g/dL	31 (20-44	32 (27-75)	31 (20-44)
Median haemoglobin (range), g/dL	12.8 (8.1-16.5)	12.3 (10.8-16.5)	12.8 (8.1-16.5)
Median platelet count (range), $x10^3/\mu L$	79 (15-294)	46 (29-195)	81 (15-294)
Median bilirubin (range), µmol/L	22 (4-117)	25 (8-86)	22 (4-117)
History of decompensation, n (%)	32/101 (31.7)	3/8 (37.5)	29/93 (31.3)
MELD score (range),	10 (6-24)	11 (10-24)	10 (6-23)
0-9, n (%)	34/84 (41.7)	-	35/78 (44.9)
10-15, n (%)	40/84 (47.6)	4/6 (66.6)	36/78 (46.1)
16-21, n (%)	7/84 (8.3)	1/6 (16.7)	6/78 (7.7)
21+, n (%)	2/84 (2.4)	1/6 (16.7)	1/78 (1.3)
HCV Genotype			
1a, n (%)	29/101 (28.7)	4/8 (50)	25/93 (26.9)
1b, n (%)	19/101 (18.8)	-	19/93 (20.4)
1 (no subtype), n (%)	27/101 (26.7)	-	27/93 (29)
2, n (%)	-	-	-
3, n (%)	24/101 (23.8)	4/8 (50)	20/93 (21.5)
4, n (%)	1/101 (1)	-	1/93 (1.1)
Mixed, n (%)	1/101 (1)	-	1/93 (1.1)
Treatment experienced, n (%)	51/101 (50.5)	1/8 (12.5)	50/93 (53.8)
Dual therapy, n (%)	39/101 (38.6)	1/8 (12.5)	38/93 (40.9)
PI/PR, n (%)	12/101 (11.9)		12/93 (12.9)
Child-Pugh Score			
A, n (%)	15/101 (14.9)	-	15/93 (16.1)
B, n (%)	67/101 (66.3)	4/8 (50)	63/93 (67.8)
C, n (%)	19/101 (18.8)	4/8 (50)	15/93 (16.1)
HIV Co-infected, n (%)	17/101 (16.8)	2/8 (25)	15/93 (16.1)
Median baseline HCV-RNA IU/ml (range)**	366126 (0-5897884)	137970 (0-574654)	408888 (0-5897884)

MELD = Model for end-stage liver disease, IQR = interquartile range, ALT = alanine aminotransferase
*Missing data are a common problem with observational data. Percentages are calculated based on the proportion of available data.
** Three patients that commenced treatment were later found to have undetectable viremia at baseline. These patients had previously presented with detectable HCV-RNA.

5.6.1 Effectiveness

The rate of SVR12 obtained for this cohort was 74% (n=75/101). There was a statistically significant difference in the SVR12 rate in GT1-infected patients compared with GT3-infected patients (87% (n=65/75) vs. 42% (n=10/24), p<0.0001) (Table 16). Given the poor response of GT3 patients to treatment with SOF/LDV±RBV for 12 weeks (the treatment duration stipulated in the terms of the EAP by the manufacturer),

and following on from the revised EASL 2015 guidelines [122], SOF/LDV±RBV is no longer recommended for use in GT3 patients.

Table 16: Treatment outcomes stratified by genotype for patients treated with SOF/LDV±RBV under the EAP

	GT1 n=75		GT3 n=24		GT4 n=1		Mixed GT n=1		Total n=101	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
SVR12	65/75	87	10/24*	41.7	-	-	-	-	75/101*	74.3
Relapse rate	4/75	5	9/24	27.5	1/1	100	1/1	100	15/101	14.9
Lost to follow-up	1/75	1	-	-	-	-	-	-	1/101	1
Discontinuation rate	5/75	7	6/24	25		-	-	-	11/101	10.9

**One patient discontinued treatment prematurely but achieved a SVR12 - This patient is included in both the discontinuation and SVR calculations.*

5.6.2 Safety and Tolerability

The premature discontinuation rate was 11% (n=11/101) in this cohort, of whom 8 patients (8%) died while receiving treatment. Reasons for discontinuation in the remaining three patients included non-compliance with the treatment regimen (n=1), unexpected undetectable HCV-PCR at baseline (n=1, discontinued after three weeks of therapy), and relapse into drug use (n=1).

Our on-treatment mortality rate was considered high and thus, prompted a closer examination of the baseline demographics and HCV characteristics of the eight patients (Table 15). The median age was 50 years. All received treatment with SOF/LDV+RBV. GT1a and GT3 were represented in a 1:1 ratio. Four of these patients had CTP B cirrhosis at baseline, which represented 6% of all patients with CTP B. The remaining four patients were CTP C and represented 21% of all CTP C patients in this cohort. While the subgroups were too small to determine statistical significance, the mean platelet count in those who deceased on treatment (46 $x10^3$/µL) was significantly lower than in those patients who survived treatment (81 $x10^3$/µL). The causes of death for the eight patients were liver failure (n=2), intracerebral haemorrhage (n=2), sepsis (n=2), complications from pre-existing HCC (n=1) and cardiac arrest (n=1). Of note,

while there were 8 on treatment deaths, there was no mortality in the 12 weeks post-treatment through to SVR12 and provides evidence to justify further trials to study the use of these treatment regimens in patients with CTP cirrhosis.

5.6.3 Subgroup Analysis

Subgroup analysis was completed to compare the SVR12 rates between patients with CTP A, B or C. The SVR rate in patients with CTP A, B and C cirrhosis was 60% (n=9/15), 82% (n=55/67) and 58% (n=11/19), respectively. There was a statistically significant difference in the SVR12 rate between the three groups (*p*=0.049). The rate of premature discontinuation was highest in those with CTP C cirrhosis, with 21% (n=4) ceasing treatment early as a result of on-treatment mortality (Figure 26).

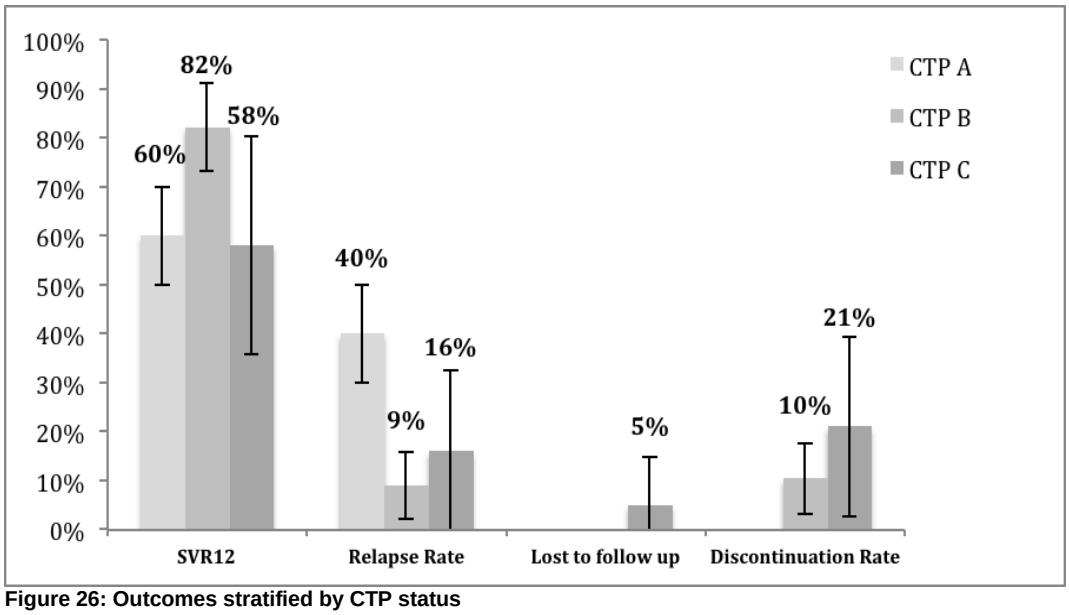


Figure 26: Outcomes stratified by CTP status

5.6.4 Comparison with Other Clinical Studies

At present, one clinical trial, SOLAR-1, has been published which reported the efficacy and safety of SOF/LDV+RBV in patients with advanced liver disease, including those with decompensated cirrhosis [304]. The baseline demographics of the patients included in the SOLAR-1 study were compared with the patients treated under the Irish EAP

(Table 17). SOLAR-1 included a cohort of GT1-infected patients with CTP B or CTP C cirrhosis randomised to treatment with 12 or 24-weeks of SOF/LDV+RBV. In the EAP, the patients were younger, had a statistically significantly lower proportion of patients with GT1 HCV infection (p=0.0008) and a lower proportion of patients with CTP C cirrhosis (p=0.0198). SOLAR-1 did not include any patients with GT3 HCV infection or patients with CTP A cirrhosis.

Table 17: Key baseline demographic and HCV characteristics for patients treated in the SOLAR-1 clinical trial or and Irish EAP

	Irish EAP n=101	**SOLAR-1 CTP B n=30**	**SOLAR-1 CTP C n=21**
Median age (IQR), yrs.	54 (47-61)	60 (53-63)	58 (53-61)
Male, (%)	64.4	73	61
MELD score (range),	10(6-24)	N/A	N/A
0-9, n (%)	(42/101) 42	(6/30) 20	-
10-15, n (%)	(49/101) 48	(21/30) 70	(15/21) 70
16-21, n (%)	(8/101) 8	(3/30) 10	(6/21) 30
21+, n (%)	(2/101) 2	-	-
HCV Genotype			
1a, n (%)	(75/101) 74	(29/30) 97	(19/21) 91
1b, n (%)			
1 (no subtype), (%)			
2, n (%)	-	-	-
3, n (%)	(24/101) 24	-	-
4, n (%)	(1/101) 1	(1/30) 3	(2/21) 9
Mixed, (%)	(1/101) 1	-	-
Treatment experienced, n (%)	(51/101) 51	(22/30) 73	(10/21) 48
Dual therapy, n (%)	(39/101) 39	(10/30) 33	(7/21) 35
PI/PR, n (%)	(12/101) 12	(9/30) 30	(2/21) 9
Other, n (%)	-	(3/30) 10	(1/21) 4
Child-Pugh Score			
A, n (%)	(15/101) 15	-	-
B, n (%)	(67/101) 66	(27/30) 90	(6/21) 30
C, n (%)	(19/101) 19	(3/30) 10	(15/21) 70

IQR = interquartile range, PI/PR = protease inhibitor + pegylated interferon and ribavirin
N/A = Not available

In SOLAR-1, the SVR12 rate in patients with CTP B cirrhosis treated for 12 weeks (n=30) was 86% while 10% relapsed following treatment and one patient died on treatment. In those with CTP C cirrhosis treated for 12 weeks (n=21), the SVR12 was 85%. One patient relapsed following treatment and one patient died while on treatment.

Figure 27 compares the SVR12 rates between patients with GT1 HCV infection in the SOLAR-1 study and the Irish EAP. The SVR12 rate for GT1-infected patients with CTP C cirrhosis in SOLAR-1 was greater than in the Irish EAP however, there was no statistically significant difference the SVR12 rates in the CTP B (*p*=0.74) and CTP C (*p*=0.55) cohorts between the two studies.

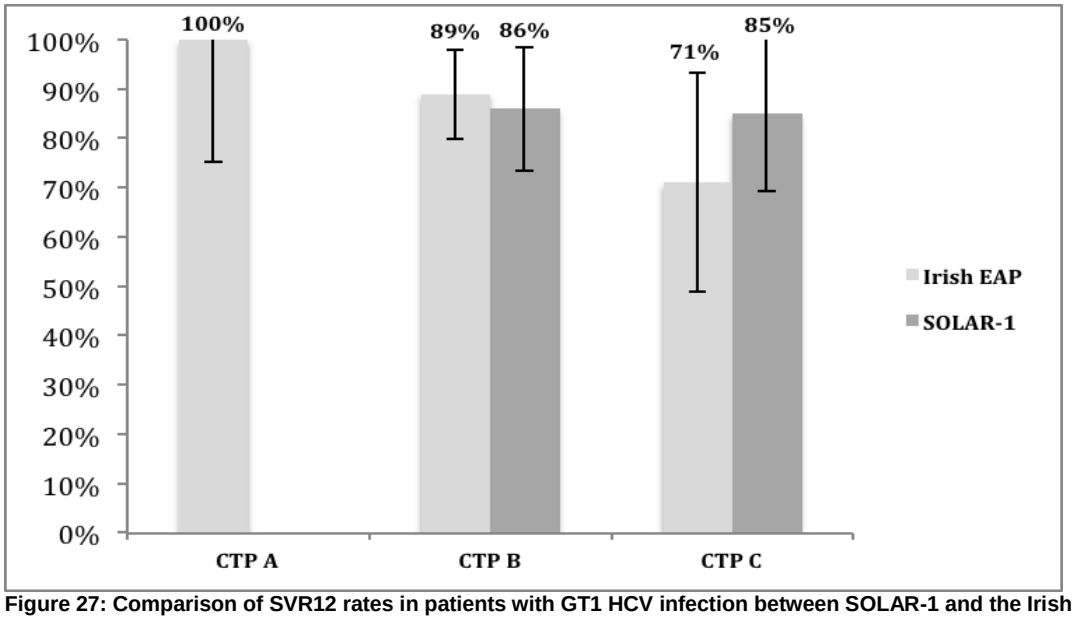


Figure 27: Comparison of SVR12 rates in patients with GT1 HCV infection between SOLAR-1 and the Irish EAP
**Note: No patient with CTP A cirrhosis was included in the SOLAR-1 study.*

5.6.5 Comparison with the Real World NHS Early Access Program

The baseline demographics of the 101 patients treated under the Irish EAP were compared to the National Health Service (NHS) EAP in the UK [330]. The Irish EAP had a higher proportion of patients with GT1 infection (75% vs. 49%; *p*=0.002) and fewer that were treatment-experienced (51% vs. 61%; *p*=0.06). The prevalence of patients with CTP C cirrhosis was higher in the Irish cohort (19% vs. 9%; *p*=0.005) (Table 18).

Table 18: Key baseline demographic and HCV characteristics for patients treated in the Irish and NHS EAP

	Irish EAP n=101	**NHS EAP n=467**
Median age (IQR), yrs.	54 (47-61)	54 (28-80)[#]
Male, (%)	64.4	73
MELD score (range),	10(6-24)	11 (6-32)
HCV Genotype		
1a, n (%)	(75/101) 74	(231/467) 50
1b, n (%)		
1 (no subtype), n (%)		
3, n (%)	(24/101) 24	(192/467) 41
Other	(2/101) 2	(44/467) 9
Treatment experienced, n (%)	(51/101) 51	(284/467) 61
Dual therapy, n (%)	(39/101) 39	(267/467) 57
PI/PR, n (%)	(12/101) 12	(17/467) 4
Other, n (%)	-	-
Child-Pugh Score		
A, n (%)	(15/101) 15	(105/467) 23
B, n (%)	(67/101) 66	(319/467) 68
C, n (%)	(19/101) 19	(43/467) 9

IQR = interquartile range, PI/PR = protease inhibitor + pegylated interferon and ribavirin
#The range around the median age was provided but no IQR.

Overall, the SVR12 rate in the Irish EAP was lower than in the NHS EAP (74% vs. 82%; *p*=0.093)). However, in the GT1-infected cohorts, the SVR12 rates were broadly similar, 87% in the Irish EAP and 92% in the NHS EAP (*p*=0.349).

Our on-treatment mortality rate was twice the rate of both the NHS EAP study (8% vs. 3.6%; *p*=0.057) and the SOLAR-1 study (8% vs. 3.8%; *p*=0.334). This highlights the concerns there are with treating this cohort of patients with advanced liver disease in the real world. On-treatment mortality in patients with CTP B cirrhosis at baseline was 6%, whereas the mortality in those with CTP C cirrhosis was 21%.

5.7 Discussion – Sub-study 2

In the cohort of HCV-infected individuals with advanced liver disease and/or decompensated cirrhosis treated with SOF/LDV±RBV for 12 weeks, the rate of SVR12 was 74%. However, the SVR12 rate in the GT3 HCV infected subgroup was 42%,

which when compared to the SVR12 rate of 87% in the GT1 subgroup, resulted in the lower overall SVR12. The low SVR12 rate in GT3-infected individuals was due to the fact that these patients were treated with a combination regimen that included ledipasvir, a DAA found to have low antiviral activity in GT3-HCV infection, and therefore, these patients were being under-treated. The discontinuation rate was 11% of whom eight died while receiving treatment. Thus, as anticipated, discontinuation owing to non-compliance, AEs and other factors was considerably lower than in the IFN-based cohort of patients, where discontinuation rates ranged between 26% and 38%. This was due to the lower side-effect profile and shortened duration of treatment of the IFN-free combination regimens. The mortality rate of 8% was considered high and further investigation revealed that 6% of all patients included in this cohort with CTP B cirrhosis died while receiving treatment. Of greater concern was the fact that 21% of patients with CTP C cirrhosis died while receiving treatment suggesting that in patients with advanced liver disease, in particular those with CTP C cirrhosis, antiviral therapy carries a significant risk and clinicians should consider very carefully the risk/benefit of therapy versus rapid transplantation in such patients.

When we compared the overall SVR12 rate from this sub-study with the outcomes reported in the SOLAR-1 clinical trial, the lower SVR12 in our study is attributed to the treatment of a cohort of GT-3 infected patients with a combination regimen that included ledipasvir as per the Summary of Product Characteristics (SPC). However, ledipasvir was subsequently found to demonstrate low antiviral activity in GT3 infection and was removed from the list of recommended GT3 regimens in 2015 [7, 122]. When we compared the outcomes in GT1-infected individuals exclusively, the SVR12 rate in CTP B patients was comparable but was lower in patients with CTP C cirrhosis in our study. The high mortality rate in our study can explain for this difference.

There was particular interest in comparing the outcomes in our decompensated cohort study with the NHS EAP, considering both studies applied identical inclusion criteria [330, 361]. While the overall SVR12 rate in the Irish EAP was lower than the rate in the NHS EAP study, the SVR12 rate in GT1-infected patients treated with SOF/LDV±RBV in the two studies was comparable. With a higher proportion of patients with CTP C cirrhosis included in the Irish EAP, the on-treatment mortality rate was approximately twice that of the NHS EAP. As result of this analysis, treatment guidelines in Ireland were amended and patients with advanced liver disease (CTP C) were no longer considered suitable for treatment and were instead referred to the national transplantation unit for assessment.

5.8 Results – Sub-study 3

Between April 2015 to July 2016, 205 patients with compensated cirrhosis (CTP A) had completed treatment (to SVR12 or premature discontinuation) with IFN-free regimens, of whom n=150 were GT1 (73%), n=3 were GT2 (1.5%), n=41 were GT3 (20%), n=10 were GT4 (5%) while one patient was classified as mixed GT (0.5%). The majority of patients were male (65%) and between the ages of 40 and 64 years (76%) with a median age of 51 (IQR 45-60). A MELD score less than 10 was present in 83% of the cohort. A high proportion of patients had failed to respond to, or relapsed following, previous HCV treatment (44%); 30% failed to respond to, or relapsed following, treatment with PR treatment and 14% had failed to respond to, or relapsed following, treatment with a first-generation protease inhibitor triple therapy combination, TPV/PR, BOC/PR or SMV/PR (Table 19).

Table 19: Baseline demographics of the n=205 patients with compensated cirrhosis treated with IFN-free regimens

	Total* n=205	SOF/LDV±RBV* n=74	3D±RBV* n=83	SOF/DCV±RBV* n=48
Median age (IQR), yrs.	51 (45-60)	52 (46-61)	55 (47-62)	48 (42-54)
18-39, n (%)	22/205 (10.7)	8/74 (10.8)	6/83 (7.2)	8/48 (16.6)
40-64, n (%)	156/205 (76.1)	55/74 (74.3)	63/83 (75.9)	38/48 (79.2)
≥65, n (%)	27/205 (13.2)	11/74 (14.9)	14/83 (16.9)	2/48 (4.2)
Male, n (%)	133/205 (64.9)	49/74 (66.2)	50/83 (60.2)	34/48 (70.8)
Median ALT (IQR), *IU/L*	78 (51-124)	75 (53-126)	70 (48-105)	96 (51-161)
Median albumin (IQR), g/dL	40 (36-43)	41 (37-43)	39 (34-43)	39 (35-43)
Median haemoglobin (IQR), g/dL	14.1 (13.5-15.6)	14.1 (13.6-15.4)	14 (13.5-15.8)	14.5 (13.8-15.7)
Median platelet count (IQR), $x10^3/\mu L$	130 (83-166)	142 (86-180)	127 (93-167)	112 (67-148)
Median MELD score (IQR)	7 (6-9)	7 (6-9)	7 (6-9)	7 (6-9)
0-9, n (%)	108/130 (83.1)	36/43 (83.7)	47/55 (85.5)	25/32 (78.1)
10-15, n (%)	18/130 (13.9)	7/43 (16.3)	4/55 (7.3)	7/32 (21.9)
16-21, n (%)	2/130 (1.5)	-	2/55 (3.6)	-
21+, n (%)	2/130 (1.5)	-	2/55 (3.6)	-
HCV Genotype, n (%)				
1a	67/205 (32.6)	38/74 (51.3)	29/83 (34.9)	-
1b	56/205 (27.3)	18/74 (24.3)	38/83 (44.6)	1/48 (2.1)
1 (no subtype)	27/205 (13.2)	9/74 (12.2)	16/83 (19.3)	2/48 (4.2)
2	3/205 (1.5)	-	-	3/48 (6.2)
3	41/205 (20)	-	-	41/48 (85.4)
4	10/205 (4.9)	8/74 (10.8)	1/83 (1.2)	1/48 (2.1)
Mixed	1/205 (0.5)	1/74 (1.4)	-	-
Treatment experienced, n (%)	89/202 (44.1)	38/74 (51.4)	33/80 (41.3)	18/48 (37.5)
Dual therapy	61/202 (30.2)	18/74 (24.4)	28/80 (35)	15/48 (31.2)
PI/PR	28/202 (13.9)	20/74 (27)	5/80 (6.3)	3/48 (6.3)

IQR = interquartile range, ALT = alanine aminotransferase. PI/PR = protease inhibitor + pegylated interferon and ribavirin, CTP = Child's Turcotte Pugh score
*Missing data are a common problem with observational data. Percentages are calculated based on the proportion of available data

5.8.1 Effectiveness

5.8.1.1 Genotype 1

In GT1-infected individuals treated with SOF/LDV±RBV and 3D±RBV (n=150), the overall SVR12 rate was 89%, 89% in GT1 (no subtype), 87% in GT1a patients and 91% in GT1b. SVR12 rates were 88% for SOF/LDV±RBV and 90% for 3D±RBV (Table 20). Three GT1-infected individual were treated with SOF/DCV±RBV, two achieved a SVR12 and the remaining patient had not returned for a SVR12 assessment and was considered lost to follow-up. The odds of a SVR12 in a patient treated with 3D±RBV was 1.3 times the odds of a SVR12 in those treated with SOF/LDV±RBV (OR=1.3, *p*=0.622, 95% CI 0.459-3.67). The proportion of patients who relapsed was higher amongst the SOF/LDV±RBV cohort (4.6%, n=3/65) compared with the 3D±RBV cohort (2.4%, n=2/82). Overall, seven patients discontinued treatment prematurely. Two patients who died on treatment were categorised as discontinuing treatment prematurely and having failed to achieve a SVR12. Seven patients were considered lost to follow-up. These patients completed a full course of therapy but failed to return for a SVR12 assessment.

Table 20: Treatment outcomes stratified by regimen for patients with genotype 1 HCV infection

	SOF/LDV±RBV n=65		**3D±RBV n=82**		**SOF/DCV±RBV n=3**		**Total n=150**	
	n/N	%	n/N	%	n/N	%	n/N	%
SVR12, n (%)	57/65[#]	87.7	74/82[#]	90.2	2/3	66.7	133/150[#]	88.7
Relapse rate, n (%)	3/65	4.6	2/82	2.4	-	-	5/150	3.3
Lost to follow-up, n (%)	3/65	4.6	3/82	3.7	1/3	33.3	7/150	4.7
Discontinuation rate, n (%)	3/65	4.6	4/82	4.9	-	-	7/150	4.7

Two patients, one treated with SOF/LDV±RBV and one with 3D±RBV discontinued treatment prematurely but subsequently achieved a SVR12.

5.8.1.2 Genotype 3

All GT3-infected individuals (n=41) were treated with SOF/DCV±RBV for 24 weeks in accordance with current recommendations. The SVR12 rate for this cohort of patients was 85% (n=35/41). There were no patients who relapsed following treatment completion. Premature treatment discontinuation occurred in 12% (n=5/41) (Table 21).

Table 21: Treatment outcomes for patients with genotype 3 infection

	Total n=41	
	n/N	%
SVR12, n (%)	35/41	85.4
Relapse rate, n (%)	-	-
Lost to follow up, n (%)	1/41	2.4
Discontinuation rate, n (%)	5/41	12.2

5.8.1.3 Other Genotypes

Fourteen additional patients with GT2 (n=3), GT4 (n=10) and one with mixed GT HCV infection were treated. GT2-infected patients were treated with SOF/DCV±RBV. Eight GT4 patients were treated with SOF/LDV±RBV, one treated with 3D±RBV, one patient was treated with SOF/DCV±RBV and the remaining mixed GT patient was treated with SOF/LDV±RBV. All fourteen patients achieved a SVR12.

5.8.2 Subgroup Analysis

Overall, SVR12 rates in treatment-experienced individuals were better than in treatment naïve individuals (91% vs. 87%). The SVR12 rates in individuals previously treated with dual therapy was 93% (94% with SOF/LDV±RBV, 93% with 3D±RBV and 93% with SOF/DCV±RBV) while in those previously treated with protease-inhibitor triple therapy, the SVR12 rate was 86% (90% with SOF/LDV±RBV, 60% with 3D±RBV and 100% with SOF/DCV±RBV) (Table 22). There was no statistically significant difference in the SVR12 rates between treatment naïve and treatment-experienced

individuals irrespective of whether these patients had previously been treated with dual- or triple therapy combinations.

Table 22: SVR12 rates stratified by treatment regimen and HCV characteristics

	Total* n=205		**SOF/LDV±RBV* n=74**		**3D±RBV* n=83**		**SOF/DCV±RBV* n=48**	
	n/N	%	n/N	%	n/N	%	n/N	%
Overall	182/205	88.8	66/74	89.2	75/83	90.4	41/48	85.4
TN	98/113	86.7	31/36	86.1	43/47	91.5	24/30	80
TE	81/89	91	35/38	92.1	29/33	87.9	17/18	94.4
Dual	57/61	93.4	17/18	94.4	26/28	92.9	14/15	93.3
PI/PR	24/28	85.7	18/20	90	3/5	60	3/3	100
GT1a	58/67	86.6	32/38	84.2	26/29	89.7	-	-
GT1b	51/56	91.1	17/18	94.4	34/37	91.9	1/1	100
GT1 (no subtype)	24/27	88.9	8/9	88.9	14/16	87.5	2/2	100
GT3	35/41	85.4	-	-	-	-	35/41	85.4
GT 1 TN	69/79	87.3	26/31	83.9	43/47	91.5	1/1	100
TE	61/68	89.7	31/34	91.2	28/32	87.5	2/2	100
GT3 TN	23/28	82.1	-	-	-	-	23/28	82.1
TE	12/13	92.3	-	-	-	-	12/13	92.3

TN = Treatment naïve, TE = Treatment experienced, GT = genotype
*Missing data are a common problem with observational data. Percentages are calculated based on the proportion of available data

5.8.3 Safety and Tolerability

Ninety-four percent of the entire cohort of patients with compensated cirrhosis completed a full course of treatment. Two patients died while on therapy. The rate of discontinuation was 4% in those treated with SOF/LDV±RBV (n=3/71) and 5% in those treated with 3D±RBV (n=4/82). In the SOF/DCV±RBV cohort, 10% (n=5/48) discontinued treatment prematurely. Reasons for discontinuation are outlined in Table 23.

Table 23: Reasons for discontinuation and cause of death stratified according to treatment regimen.

	SOF/LDV±RBV n=74	3D±RBV n=83	SOF/DCV±RBV n=48
Discontinued, n (%)	3/74 (4.2)	4/83 (4.8)	5/48 (10.4)
AE	-	1/83 (1.2)	1/48 (2.1)
Non-compliance	1/74 (1.4)	-	3/48 (6.2)
HCV-PCR undetectable at baseline	1/74 (1.4)	-	1/48 (2.1)
Disease progression	-	1/83 (1.2)	-
Drug relapse	-	1/83 (1.2)	-
Death - Liver decompensation	1/74 (1.4)	-	-
Death - Drug-induced liver injury	-	1/83 (1.2)	-

AE = adverse event

Overall, the on-treatment mortality rate was 1% (n=2). Both patients were GT1-infected patients, one treated with SOF/LDV+RBV and one with treated with 3D+RBV. Both were male and co-infected with HIV. One of the two patients had previously failed treatment with protease inhibitor triple therapy. The causes of death were liver decompensation and drug-induced liver injury.

5.8.4 Propensity Score Stratification

Propensity scoring was applied to the GT1 cohort of patients treated with SOF/LDV±RBV and 3D±RBV. Prior to applying PS stratification, a comparison of confounders between the SOF/LDV±RBV and 3D±RBV groups was completed. Variables with a standardised difference greater than 0.1 indicated that there was an imbalance between the two treatment groups (Appendix 2 Table A 7).

After stratification, five strata were formed and the standardised difference for six of the seven covariates was less than 0.1 (Appendix 2 Table A 8). One covariate, previous protease inhibitor triple therapy experience, had a standardised difference of -0.117 after stratification. Despite making adjustments to the model and covariates, a standardised difference <0.1 for all covariates was not achieved. After controlling for confounding, the adjusted SVR12 rates for both SOF/LDV±RBV and 3D±RBV were

85% and 89%, respectively. The adjusted odds of SVR in patients treated with 3D±RBV were 1.09 times the odds of SVR in patients treated with SOF/LDV±RBV (OR = 1.09, *p*=0.623, 95% CI 0.76-1.51).

5.8.5 Comparison with Clinical Trials

Supporting evidence for the licensing of the IFN-free regimens for patients with compensated cirrhosis were obtained from a number of phase II/III clinical trials. Three published clinical trials included patients with GT1 infection treated with SOF/LDV±RBV, namely ION1, ION2 and SIRIUS [125, 126, 305]. One trial, TURQUOISE-II, assessed the response to 3D±RBV [130] in GT1-infected patients while the ALLY-3 study investigated the response of patients with GT3 infection to SOF/DCV±RBV [362]. The absolute difference in SVR12 rates between the SOF/LDV±RBV GT1 clinical trials and the national HCV registry GT1 dataset were -9% and 4% for ION1 and ION2, respectively and -8% for the SIRIUS study (Figure 28). The absolute difference in SVR12 rates between GT1-infected patients treated with 3D±RBV in the Irish registry study and in the TURQUOISE-II study was -4% (Figure 29). In the GT3 cohort, the absolute difference in SVR rates in the ALLY-3 study and this study was 22% (Figure 30).

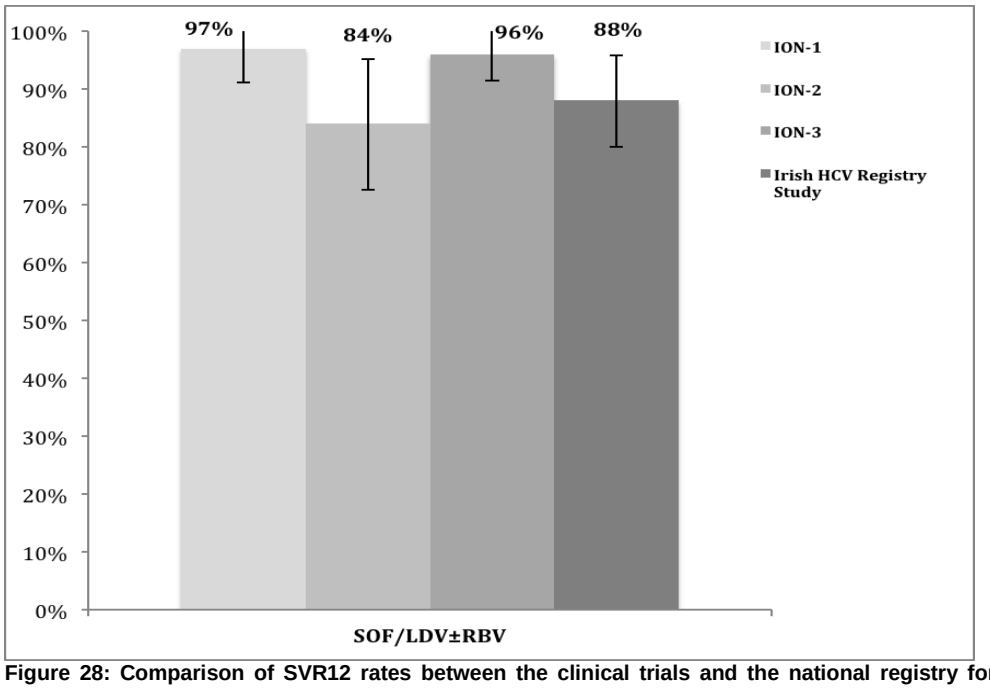


Figure 28: Comparison of SVR12 rates between the clinical trials and the national registry for GT1 infected patients with cirrhosis treated with SOF/LDV±RBV

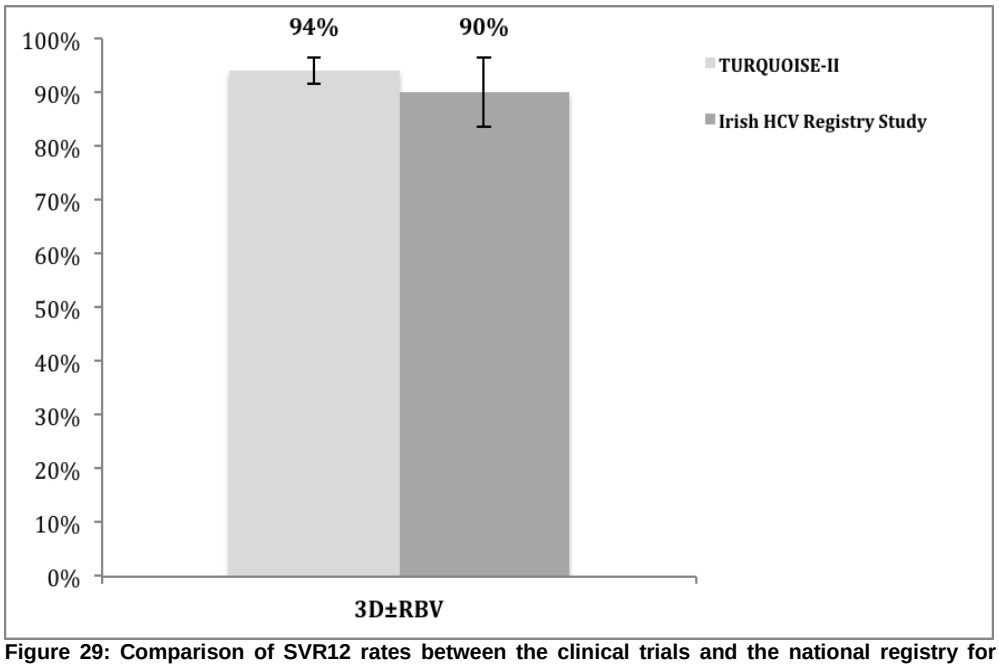


Figure 29: Comparison of SVR12 rates between the clinical trials and the national registry for GT1 infected patients with cirrhosis treated with 3D±RBV

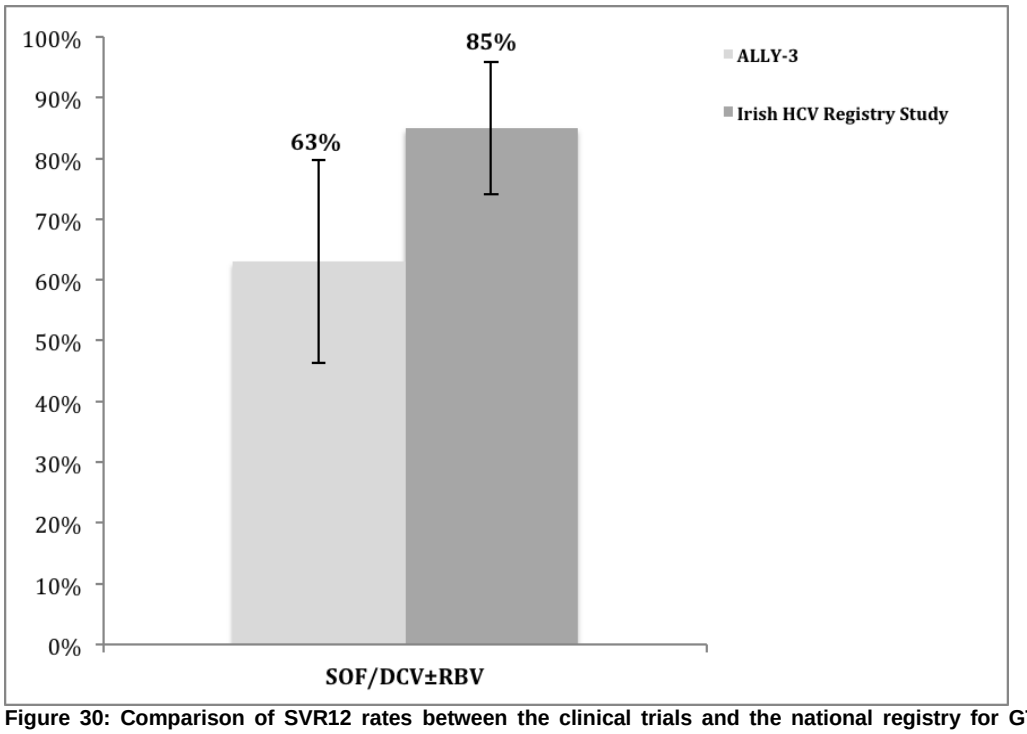


Figure 30: Comparison of SVR12 rates between the clinical trials and the national registry for GT3-infected patients treated with SOF/DCV±RBV

5.8.6 Comparison with International Real World Studies

The real world SVR12 rates in GT1-infected patients treated with SOF/LDV±RBV were reported in a number of studies [325, 363, 364]. These studies included a combination of patients with and without the presence of cirrhosis with the exception of the TRIO Health study which included patients with cirrhosis exclusively. In our study, we obtained a SVR12 rate of 88% in GT1 patients treated with SOF/LDV±RBV. When we compared this to the SVR12 rate in the subgroup of patients with cirrhosis in the US Department of Veteran Affairs (VA) (74%), HCV-TARGET (98%) and TRIO Health (86%) studies, we found that there was variation in the SVR12 rates reported between each study but that our SVR12 rate represented an average of the SVR12 rates between the other three studies (Figure 31).

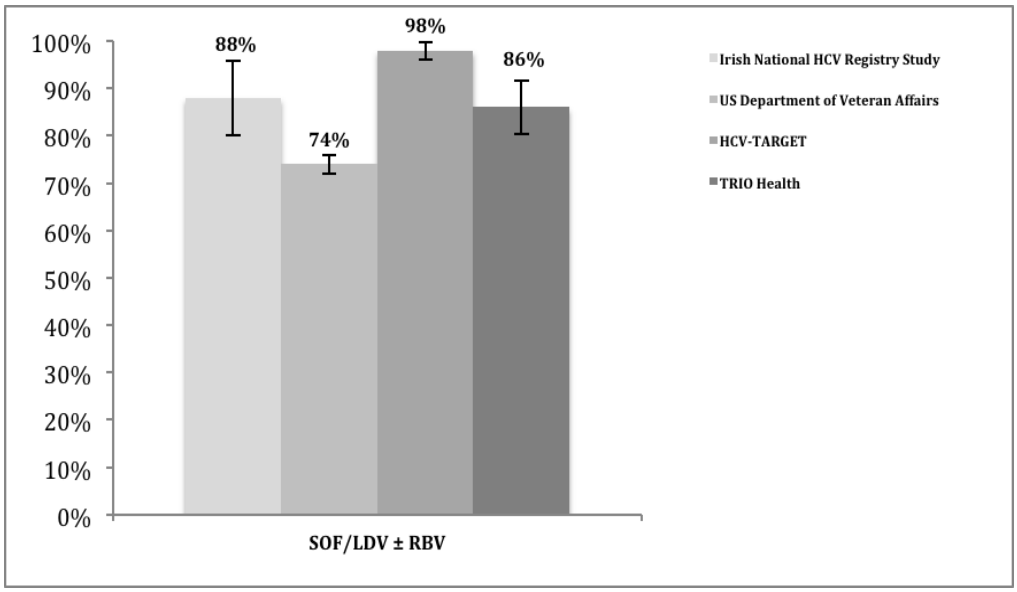


Figure 31: Comparison of the SVR12 rates between GT1 patients treated with SOF/LDV±RBV in the national registry study and other international real world studies.
While the Department of Veteran Affairs and HCV-TARGET studies include both patients with and without cirrhosis, these SVR12 rates reflect the outcomes in the subgroups with cirrhosis, exclusively.

The US Department of VA study also reported the SVR12 rate in a cohort of GT1 patients treated with 3D±RBV, of whom 27% had cirrhosis. The SVR12 rate in the subgroup with cirrhosis was 85%, lower than the 90% we reported in this study (Figure 32) [363].

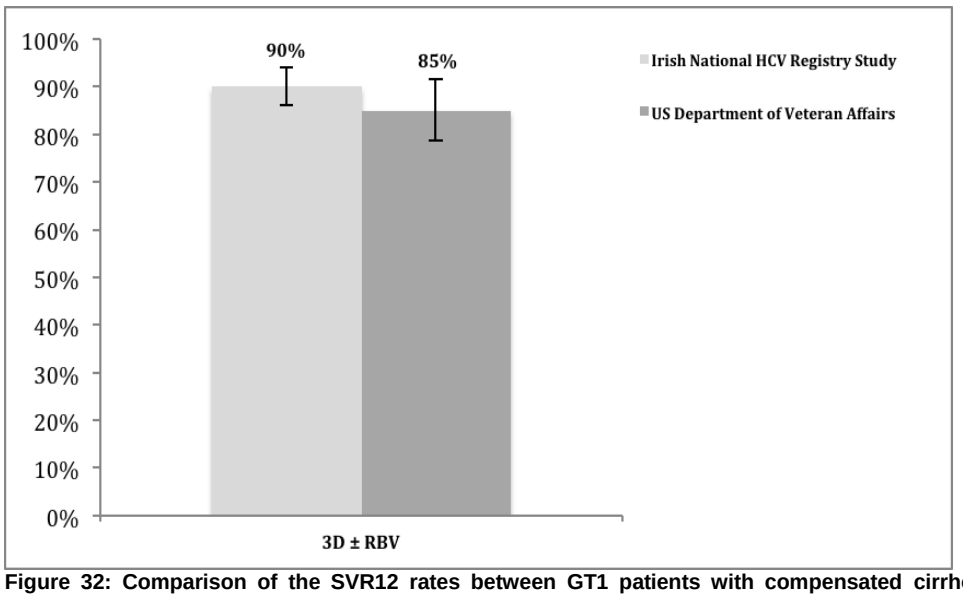


Figure 32: Comparison of the SVR12 rates between GT1 patients with compensated cirrhosis treated with 3D±RBV in the national registry and the US Veteran Affairs study
The SVR12 rates reported for the US Department of Veteran Affairs study represents the SVR12 rate in the subgroup of patients with cirrhosis.

5.9 Discussion – Sub-study 3

In the cohort of patients with compensated cirrhosis, the SVR12 rate for patients treated with SOF/LDV±RBV was 89%. It was found that the SVR12 rate was higher in treatment-experienced patients when compared to those without previous treatment experience (92% vs. 85%) but this difference was not statistically significant, demonstrating that previous treatment experience does not have the same impact on the SVR12 rate in IFN-free regimens as it did in the IFN-based regimens. It is also possible that those with previous treatment experience are more compliant with the IFN-free regimens, which resulted in increased SVR12 rates. 3D±RBV was licensed for use in GT1-infected patients without cirrhosis or with compensated cirrhosis. The SVR12 rate for 3D±RBV in this study was 90%, 92% in treatment naïve and 88% in treatment-experienced patients. With SOF/DCV±RBV, the SVR12 rate was 85% in GT3-infected patients, while four additional patients (GT2 (n=3) and GT4 (n=1)) treated with SOF/DCV±RBV each achieved a SVR12. In treatment naïve and treatment-experienced patients, the SVR12 was 83% and 92%, respectively.

The premature discontinuation rate was 6% in this study, from which two patients died. The mortality rate of 1% is considerably lower than the mortality rate of 8% reported in our EAP cohort and the NHS EAP (3.6%), which both included a number of patients with CTP C cirrhosis and/or decompensated cirrhosis [330, 361]. This demonstrates that the tolerability to IFN-free treatment is better in patients with CTP A cirrhosis and it reinforces the fact that patients with CTP C cirrhosis need to be very carefully considered before and monitored closely during treatment with DAA therapy, if commencing treatment at all.

In the HCV-infected individuals with compensated cirrhosis treated with one of three IFN-free regimens in accordance with best-practice guidelines (SOF/LDV±RBV, 3D±RBV or SOF/DCV±RBV), we observed SVR12 rates broadly similar to those reported in clinical trials. These results represented real world effectiveness in a population of patients with compensated cirrhosis, where a large proportion (44%) had previously failed to respond to treatment and so, these patients were once considered difficult-to-treat.

A comparison of the SVR12 rates between the GT1 population in clinical trial and our GT1 patient population demonstrated a high cure rate amongst treated patients, although there was a small numerical reduction in the rate of SVR12 obtained. The highest rate of concordance between RCTs and the real world setting was obtained for 3D±RBV. This may be attributable to the careful selection of patients required for treatment with this regimen as defined in the SPC. Additionally, the comparable SVR12 rates for all regimens may reflect the intensive involvement of the pharmacist in completing an in-depth assessment of potential drug interactions and appropriate follow-up and/or monitoring.

In the forty-one GT3-infected patients, the overall SVR12 rate was 85%, all of whom were treated with SOF/DCV±RBV for 24-weeks and was significantly higher than the SVR12 rate reported in the ALLY-3 trial [362]. However, this is likely explained by the 12-week duration of treatment in the ALLY-3 trial with clinical guidelines subsequently recommending the treatment with SOF/DCV±RBV for 24 weeks.

The GT1 cohort with compensated cirrhosis treated with SOF/LDV±RBV or 3D±RBV demonstrated comparable SVR12 rates with patients in other real world studies. In

those treated with SOF/LDV±RBV, our SVR12 rate was higher than that reported in the US Department of VA study. Patients in the VA study were, on average, 8 years older than those in our study and included a considerably greater proportion of males. The SVR12 rate in the HCV-TARGET study was 10% higher than our SVR12 rate (98% vs. 88%). The patient demographics in these two studies are comparable and no reason for the difference can be identified. The SVR12 rate in our cohort of GT1 patients treated with 3D±RBV was greater than the rate in the US Department of VA study (90% vs. 85%). Given that there was a higher proportion of patients with previous treatment experience and a lower proportion of males included in our study, we cannot attribute the lower SVR12 rate in the VA study to a higher proportion of difficult-to-treat patients and it may be due to the careful consideration and selection of patients for treatment with 3D±RBV in the Irish national registry.

5.10 General Discussion on Clinical Effectiveness

There was a substantial degree of concordance in the SVR12 and SVR24 rates between RCTs and the real world setting in Ireland for both IFN-based and IFN-free regimens. This importantly suggests that routine clinical practice among prescribing physicians and CNSs in Ireland is associated with comparable rates of SVR12 and SVR24 compared to the highly intensive clinical trial management pathways. This suggests that there is a high standard of care provided to patients in the treatment units in Ireland.

This study also demonstrated the use of propensity scoring, one of a number of tools that can be used to address the limitation due to confounding in non-randomised studies. It enables one to design and analyse an observational study so that it mimics some of the particular characteristics of a RCT [203]. Random allocation of treatment ensures that treatment status will not be confounded by measured or unmeasured

baseline characteristics. This allows conclusions to be made about the effect of treatment on outcomes by making direct comparisons between treated and untreated subjects, or between two treatment groups. This study used PS matching or PS stratification to reduce selection bias, or confounding, whereby the treatment selected for a subject is influenced by his/her baseline demographics or disease characteristics, which may also influence the treatment outcome.

Prior to implementing PS matching in the cohort of patients treated with TPV/PR and BOC/PR, there was an imbalance between the identified confounding variables in the two treatment groups. Prior to matching, six of the nine covariates had a standardised difference greater then 0.1. We found that after propensity score matching and stratifying on the propensity score, there was a negligible difference (<0.1) in the distribution of confounders between the two treatment groups.

Three related approaches to PS matching were utilised in the TPV/PR and BOC/PR analysis; naïve matching, matching with a caliper width limit of 0.1 and matching with a caliper width limit of 0.2. Naïve matching was the first approach used. These approaches indicated no significant change in the treatment effect after matching but wide confidence intervals indicate uncertainty around the treatment effect. This is a result of our small dataset and, while PS matching is a useful tool, we acknowledge the limitations of its use in a small patient population. We suggest that propensity scoring is best applied and assessed in a larger patient population and may be more appropriate for use in the future when a larger population patients have been treated with the IFN-free regimens in Ireland.

Another approach to propensity scoring was applied in the subgroup of patients with compensated cirrhosis treated with SOF/LDV±RBV and 3D±RBV. PS stratification has advantages over PS matching because it uses all data unlike in matching, whereby the number of subjects in the comparator group limits the number of matches that will be formed. After stratification, minimal differences in the unadjusted and the adjusted SVR12 rates in the two treatment regimens were observed.

Given that the value of outcomes from clinical trials for estimating effectiveness in routine clinical practice is limited by the strict inclusion criteria and protocols applied to these trials, this study provides valuable real world data from the Irish clinical setting [174, 175]. Historically, translation of outcomes observed in clinical trials to clinical practice has been associated with lower SVR12/24 rates and higher rates of AEs. As a result, observational studies are becoming increasingly important for assessing the effectiveness of therapeutic regimens in real world clinical practice and provide valuable information regarding the effectiveness and appropriate use of agents outside of clinical trials [14, 15]. Greater importance is being placed on robust real world studies, which will underpin the clinical and policy decision-making around the use of, and reimbursement of, these treatment regimens in the clinical setting [16]. A comprehensive evidence base, including both RCTs and high-quality, well-designed observational studies, is important and can enhance reimbursement decision providing decision-makers with a greater evidence-base from which to make their assessments [11, 13, 16].

Both IFN-based and IFN-free regimens underwent evaluation for cost-effectiveness in the Irish setting, although, for the IFN-free regimens, early access was provided by the Irish healthcare provider prior to final recommendations around cost-effectiveness. In the economic analyses submitted by the manufacturers, models were populated with data from other jurisdictions and published studies that may have been associated with

uncertainty. The availability of the data obtained from this study conducted in the Irish setting provide a robust and validated input parameter base for future economic evaluations of agents for the treatment of HCV infection in Ireland. This will be of particular benefit to healthcare decision-makers involved in reimbursement decisions [16].

There are a number of strengths to these studies. They provide outcome data on a variety of treatment regimens and in diverse patient populations. Real world data, and indeed, RCT data for patients with compensated cirrhosis, and more importantly, for patients with advanced liver disease and/or decompensated cirrhosis has been limited. Undertaking this study enabled the generation of data in underrepresented patients, who are often the most complex and in greatest clinical need of treatment. Additionally, this study demonstrated the implementation of a tool that deals with one of the primary limitations associated with observational studies. Propensity scoring is a tool used to reduce selection bias, or confounding, whereby the treatment selected for a subject is influenced by his/her baseline demographics and disease characteristics, which may also influence the treatment outcome. Its usefulness will more apparent when the registry has accrued greater patient numbers.

There are some limitations to this data. Despite adhering to quality control procedures, it is possible that there were minor inaccuracies in the data. Unlike many other registries world wide, the Irish HCV treatment registry is not linked to an electronic databases and thus, there are many steps in the process between the medical team inputting the clinical notes accurately into patient charts and the EPR to inputting these data into the registry were error may occur. Furthermore, despite controlling for confounding, it remains possible that there are hidden biases as a result of unmeasured confounders that are difficult to address because the relevant

measurements are not available. Additionally, the population included in this study, when compared with other international real world studies, is considered to be small. However, this represents the number of patients treated in Ireland during the period of this work and reflects the limited treatment capacity in the seven treatment units in Ireland. Therefore, the numbers of patients included in some subpopulations in this study were very small and thus, may limit generalisation. In some cases, the numbers were too small to allow for meaningful analysis. While acknowledging these shortcomings in our data, we are confident that it presents accurate and validated outcomes that have been, and will be, useful for future economic evaluations of agents for the treatment of HCV.

In the context of this work, it is important to recognise is that, unlike clinical trials, the choice of treatment regimen in these studies is at the discretion of the treating physician. In sub-study 1, we observed a substantial difference in the SVR rates reported for patients treated with TPV/PR (74%), BOC/PR (60%) and SMV/PR (45%). With TPV/PR, patients received 12 weeks of TPV and is associated with some severe side effects. With BOC/PR, patients receive 24-44 weeks of BOC and the side effects, while significant, are not considered to be as severe. Therefore, physicians will have considered the profile and history of each patient before they chose, what they believed, was the most appropriate treatment. The lower rate of effectiveness in patients treated with BOC/PR was largely due to a higher discontinuation rate – patients were demonstrating poor tolerability to BOC/PR. SMV/PR was approved after TPV/PR and BOC/PR. It is possible that the poor effectiveness was as a result of patients having more advanced disease, as a result of waiting longer for treatment, and because universal Q80K mutation testing was not universally carried out.

The ability for physicians to choose a treatment for patients is important and should be considered carefully. The differences in effectiveness between the three IFN-based regimens would suggest potentially inappropriate treatment selection. While these regimens are no longer (or are rarely) prescribed, it provides evidence to support the development of algorithms or guidelines which would ensure patients, irrespective of their treating physician, receive the treatment regimen most appropriate to their profile and history. This has particular relevance at present as models of care for community-based HCV treatment are investigated. As the number of treatment centres increases, it is important that a patient would receive a treatment regimen (the most appropriate one) irrespective of which treatment centre or which physician he/she attended.

5.11 Conclusion

Data reported in this study confirms that the effectiveness of HCV treatment regimens in the real world clinical setting in Ireland is generally comparable with the efficacy rates reported in clinical trials, taking into account that historically, translation of outcomes from clinical trials is lower than in real world settings. The findings provide new data on populations under-represented in RCTs. This study provides robust information fundamental for input into future economic evaluations for agents used for the treatment of HCV infection. It is important that healthcare decision-makers aggregate all available data, from both RCTs and real world studies, when assessing the evidence and making decisions which will inform health policy and impact a large cohort of patients and their healthcare providers. This study demonstrates the application of a valuable tool, propensity scoring, which can be applied to other populations included in the national HCV registry, or to other observational research datasets worldwide.

Chapter 6

Chapter 6 The Real World Healthcare Costs Associated with Interferon-based and Interferon-free DAA Treatment for Chronic Hepatitis C Infection.

This chapter reports results from three separate sub-studies. Sub-study-1 reports the direct healthcare costs associated with the treatment of HCV infection with IFN-based and IFN-free DAA regimens. This study was accepted for publication in the Journal of Viral Hepatitis in January 2016 [365]. Sub-study 2 reports the HCV-related healthcare costs following achievement of a SVR12/SVR24 after treatment with IFN-based and IFN-free DAA regimens and sub-study 3 reports direct HCV-related healthcare costs following premature treatment discontinuation. Given a phased treatment strategy was implemented in Ireland in December 2014 to ensure appropriate allocation of resources, patients were prioritised for IFN-free treatment based on clinical need. Thus, the patients treated with IFN-free regimens in all sub-studies were those with advanced liver disease. Given the low premature discontinuation rate in those treated with IFN-free regimens, sub-study 3 includes a cohort of patients treated with IFN-based therapy exclusively.

6.1 Introduction

In recent years, DAA agents underwent economic evaluation for cost-effectiveness in Ireland, as in other healthcare jurisdictions. For these assessments, input data from various sources were used to estimate the costs and consequences of HCV treatment, as data from Ireland were not available. Similar to other healthcare systems worldwide, there are, and continue to be, significant concerns about the potential budget impact of these agents, given the burden of HCV disease and the high acquisition cost of the new therapies [82]. This has led to various jurisdictions worldwide initiating robust negotiations with manufacturers in order to reduce these costs. These have been successful in certain cases and negotiations are commencing in Ireland this year [366].

As previously described, with the introduction of the first generation protease inhibitors, a national HCV treatment registry was established with the aim of collecting clinical and economic outcomes to determine the real world impact of these treatments in the post-reimbursement era. The registry aids the collection of rich, observational, real world data, allowing the direct costs of treating HCV infection in the current hospital-based ambulatory model of care to be estimated.

While the potential budget impact of these DAA agents is considerable and raises the issue of affordability, studies have shown that untreated HCV can lead to cirrhosis, hepatic decompensation and the development of HCC [37, 39]. The incidence of these late stage complications associated with HCV is a major contributor to the economic burden associated with the disease [367]. A number of studies undertaken in both the US and in Europe have shown the high level of both direct medical costs and indirect medical costs associated with HCV [75, 78, 368-371]. Projecting the long-term clinical and cost consequences associated with HCV disease progression is a necessary requirement for the evaluation of new technologies for the treatment of chronic HCV [372]. Several studies have estimated HCV-associated healthcare costs and disease burden in different countries [75, 78, 81, 140, 368, 371, 373, 374]. More recently, a number of studies have estimated HCV-related treatment costs with DAA therapies and follow-up costs for patients with SVR with evidence suggesting that a SVR in HCV-infected individuals results in cost-saving following 'cure' [141, 365, 375-379].

Despite this, the transferability of economic outcomes between jurisdictions is limited as health systems, structures of healthcare provision and costs differ considerably between countries [141]. Cost effectiveness evaluations have frequently relied on the use of data that may not reflect real world effectiveness and resource utilisation due to the absence of local data. Healthcare decision-makers who have responsibility for

reimbursement decisions are increasingly seeking such real world outcome and cost data to inform their decisions, or to modify those decisions in the post-reimbursement period. Real world data provides useful information to enhance robust reimbursement decisions [16]. The increasing availability of real world cost data will benefit the preparation of submissions to HTA agencies, decision-makers involved in the reimbursement process and as a continuum in the life-cycle of the HTA [380]. These decision-makers are placing increased emphasis on the value of real world outcome and cost data to inform their decisions.

A recent study in Ireland has reported on the direct costs of untreated HCV infection, identifying that the direct medical costs associated with HCV care in Ireland is substantial and increases exponentially with the progression of liver disease [81]. However, data on the direct costs of treating HCV infection with DAA agents or the costs of HCV-related treatment following premature discontinuation or achievement of a SVR12/24 have not been reported.

The aim of this study was:

- To determine the direct HCV-related healthcare cost of treating HCV infection with DAA agents in a hospital-based ambulatory care setting in Ireland, and to specifically determine the mean cost per patient and mean cost per SVR in treated patients.
- To determine if a SVR resulted in decreased or increased costs and the factors influencing these costs in the post-SVR era.
- To estimate the mean annual healthcare-related cost of premature discontinuation following virological failure, AEs, non-compliance or other miscellaneous reasons.

6.2 Methods

The Irish national HCV treatment registry captures clinical data for each patient recorded at baseline, during the period of treatment, and in the post-treatment follow-up period to SVR12/24. For all three sub-studies, a micro-costing method was employed to estimate costs using data captured on a sample of patients in the registry with the exception of the cost of inpatient admissions, where a macro-costing method using Diagnostic Related Group (DRG) costs were applied. Additional data, not routinely captured in the registry (i.e. all laboratory and diagnostic investigations, the member(s) of clinical staff with whom that patient interacted with at each visit etc.), were collected through multiple site visits, interrogation of patient charts and the EPR. The samples was selected for inclusion in each sub-study based on their data availability, which was required to include laboratory, diagnostic, referral and admission data, in order to adequately micro-cost their HCV-related healthcare costs. The analysis was performed from the perspective of the payer (the HSE in Ireland) [381, 382].

Patients were eligible for these studies if they were HCV-infected, 18 years or older and were treated with either IFN-based or IFN-free DAA regimens, irrespective of baseline presence of cirrhosis or HIV co-infection. Patients were treated with one of four treatments. These were the IFN-based regimens TPV/PR or BOC/PR, or the IFN-free regimens SOF/LDV±RBV or 3D±RBV.

Patients treated with TPV/PR and BOC/PR were those without cirrhosis or with compensated cirrhosis. Patients treated with SOF/LDV±RBV were those with compensated or decompensated cirrhosis while those treated with 3D±RBV had compensated cirrhosis. Patients treated with IFN-free regimens were treated in accordance with the criteria for prioritisation adopted by the Irish healthcare payer.

6.2.1 Sub-study 1: Direct Costs of Treatment with Interferon-based and Interferon-free Direct-Acting Antiviral Regimens for Patients with Chronic Hepatitis C Infection

For this study, patients were costed for the duration of their treatment course to completion of therapy. Completion of therapy was taken as time to the SVR12/24 assessment time point.

Resources used over the course of treatment were identified from the treatment registry. Resources identified included the following:

- HCV medication costs
- Baseline work-up of patients
- On-treatment outpatient clinical assessments and associated monitoring costs (laboratory and diagnostic investigations and HCV-PCR assays)
- On-treatment management of AEs
- On-treatment admissions
- Outpatient staff utilisation

Data pertaining to all resources were extracted from the registry. The quantity of each resource used per patient from baseline to SVR12 (for IFN-free regimens) or to SVR24 (for IFN-based regimens) was determined. Unit costs of resources were obtained from the relevant sources (Appendix 3 Table A 9) and total costs were subsequently calculated by multiplying the quantity of each resource used by the unit cost of each.

6.2.1.1 Clinical Assessment of Outpatient Clinics

Attendance at, and contact with, the outpatient clinics were identified using data recorded in the treatment registry and quantified for each patient. Three categories of clinical assessment were identified (1) baseline visits, (2) on-treatment visits and (3) telephone consultations. For each, interaction with individual clinical staff was recorded including consultant grade physicians and/or doctors-in-training, CNSs, phlebotomists and administrative staff. Baseline work-up frequently occurred over a number of months preceding treatment, and an estimate of the resources involved for both IFN-based and IFN-free regimens was calculated (Appendix 3 Table A 10 and Table A 11).

On-treatment visits were primarily managed by CNSs, while physicians were involved in on-treatment clinical assessments in a number of ways:

- Primary consultant or senior registrar involvement at decision rule time-points
- Primary consultant or senior registrar involvement when referred by CNS
- Other clinic physicians on a routine/as required basis
- Referral to other hospital services for the management of AEs (captured in on-treatment management of AEs)

Each clinical assessment where laboratory investigations were undertaken was assumed to have had phlebotomy involvement. All clinical assessments included administrative resources for scheduling of appointments, medical chart retrieval and typing referral or correspondence letters.

6.2.1.2 Timing of Patient Assessments

The time spent by staff with patients was obtained in a time and motion study previously completed by Kieran *et al* in two of the study institutions, where the time spent by staff in providing assessment to patients receiving care for HCV (pre-DAA era) was measured [81]. These data were validated in the current study by interviewing CNSs from different clinical institutions. These interviews also allowed the utilisation of nursing time for telephone encounters with patients to be estimated and validated.

6.2.1.3 Medication Use

All medications prescribed from commencement of treatment to premature discontinuation or treatment end were captured in the registry and recorded. The dose, duration of treatment and pack size were recorded, where possible. Where the information pertaining to strength or treatment duration was unavailable or incomplete, standard course was assumed. Where necessary, the SPC and/or the British National Formulary (BNF) were consulted to determine the recommended duration of treatment, and dosing.

6.2.1.4 Laboratory Investigations, Diagnostic Tests and Virological Assessments

For each outpatient clinic assessment, laboratory and diagnostic tests completed were recorded for each patient. The number of HCV-PCR tests performed over the course of treatment was quantified for each patient.

6.2.1.5 On-treatment Patient Admissions

Patient admissions were captured in the registry. For each admission, the date of admission and discharge was established to calculate the duration of stay, in addition to the reason for admission, which allowed the appropriate DRG cost to be applied.

6.2.2 Sub-study 2: Achieving a Sustained Virological Response: HCV-related Healthcare Costs Following Treatment with Interferon-based and Interferon-free DAA Regimens for Chronic Hepatitis C Infection

For this study, patients who failed to achieve a SVR12/24 (due to relapse or premature discontinuation) were excluded. The post-SVR period is defined as the 12-month period after the assessment of the SVR12 (for IFN-free regimens) or the 12-month period after the assessment of the SVR24 (for IFN-based regimens) (Figure 33).

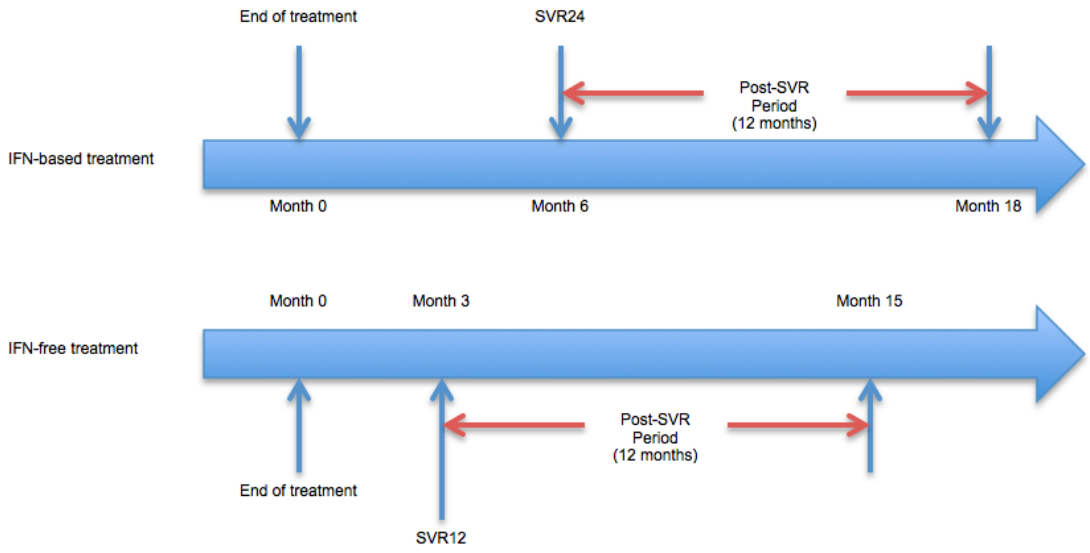


Figure 33: Timeline illustrating the 12-month post-SVR period

Clinical data were recorded for a subset of patients for a 12-month follow-up period following achievement of a SVR12 for patients treated with IFN-free regimens or a SVR24 for patients treated with IFN-based regimens. Resources used during the post-SVR period were captured through chart review and interrogation of the EPR for each patient. Resources identified included the following:

- Outpatient clinical assessments and associated costs (laboratory and diagnostic investigations and HCV-PCR assays)
- Referral to other hospital services
- HCV-related admissions

- Outpatient staff utilisation

The quantity of each resource used per patient from SVR12 (for IFN-free regimens) or from SVR24 (for IFN-based regimens), for a further 12-month period (the post-SVR follow-up period), was determined. Unit costs of resources were obtained from the relevant sources (Appendix 3 Table A 9) and total costs were subsequently calculated by multiplying the quantity of each resource used by the unit cost of each.

6.2.2.1 Clinical Assessment at Outpatient Clinics and Investigations

Attendance at the outpatient clinics in the post-SVR period was identified using data captured and quantified for each patient. Assessment by individual clinical staff was recorded, including consultant grade physicians and/or doctors-in-training, CNSs, phlebotomists and administrative staff.

During the post-SVR period, phlebotomy involvement was assumed where laboratory investigations were undertaken. All clinical assessments included costs associated with administrative resources for scheduling of appointments, medical chart retrieval and typing referral or correspondence letters. For each outpatient clinic assessment, utilisation of laboratory investigations, diagnostic tests and HCV-PCR assessments was established for each patient.

6.2.2.2 Timing of Patient Assessments

The time spent by staff with patients was obtained in a time and motion study previously completed by Kieran *et al*, where the time spent by staff in providing assessment to patients with and without cirrhosis whom achieved a SVR following HCV

treatment (pre-DAA era) was measured [81]. These data were validated by interviewing CNSs from different clinical institutions.

6.2.2.3 Patient Admissions

Patient admissions were captured through interrogation of patient charts and the EPR. For each, the date of admission and discharge was established to calculate the duration of stay. In addition, the reason for admission was recorded, which allowed the appropriate DRG cost to be applied [383]. Average costs were applied across each cohort.

6.2.3 Sub-study 3: Premature Treatment Discontinuation: HCV-related Healthcare Costs Following Treatment with Interferon-based Regimens for Chronic Hepatitis C Infection

For this sub-study, those patients who discontinued treatment prematurely were included. In those treated with IFN-free regimens, with the exception of on-treatment mortality, the premature discontinuation rate (owing to AEs, virological failure, non-compliance and other miscellaneous reasons) was low and therefore, there were insufficient patients to include in this study to allow for meaningful analysis (3%, n=8/251). As a result, this sub-study includes patients treated with IFN-based regimens, exclusively. Clinical data were collected through chart review and interrogation of the EPR for this cohort of patients for a 12-month period following the date of premature discontinuation, defined as the post-discontinuation period (Figure 34).

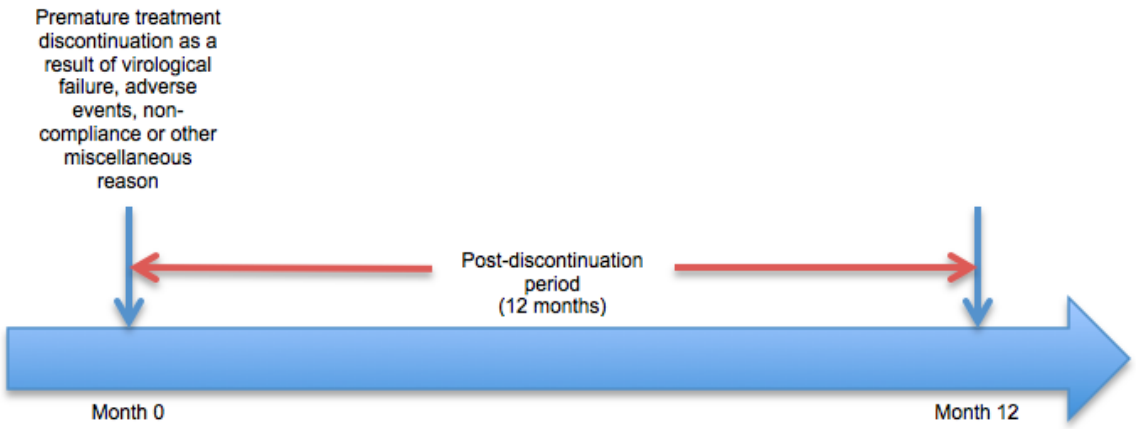


Figure 34: Timeline illustrating the 12-month post-discontinuation period

Resources used in the period following discontinuation were identified from the patient charts, EPR and registry. As in sub-study 2, the resources identified included the following:

- Outpatient clinical assessments and associated costs (laboratory and diagnostic investigations and HCV-PCR assays)
- Referral to other hospital services
- HCV-related admissions
- Outpatient staff utilisation

The quantity of each resource used per patient from the date of premature discontinuation was determined. Unit costs of resources were obtained from the relevant sources (Appendix 3 Table A 9), and total costs were subsequently calculated by multiplying the quantity of each resource used by the unit cost of each.

6.2.3.1 Clinical Assessment at Outpatient Clinics and Investigations

Attendance at the outpatient clinics was identified using data recorded in the patient charts, the EPR and the registry and assessment by individual clinical staff was recorded. For each outpatient clinic assessment, utilisation of laboratory investigations,

diagnostic tests and HCV-PCR assessments was established for each patient. Phlebotomy involvement was assumed for each laboratory investigation undertaken. Costs associated with administrative resources for scheduling of appointments, medical chart retrieval and typing referral or correspondence letters were also incorporated.

6.2.3.2 Timing of Patient Assessments

The time spent by staff with patients was obtained in a time and motion study previously completed by Kieran *et al* in two of the study institutions, where the time spent by staff in providing assessment to patients was measured [81]. These data were validated in by interviewing CNSs from different clinical institutions.

6.2.3.3 Patient Admissions

As per sub-study 1 and sub-study 2, patient admissions were captured. Data including the length of stay and the reason for admission was recorded. This allowed the appropriate DRG cost to be applied [383]. Average costs were applied across each cohort.

6.2.4 Unit cost data

For all studies, the unit cost associated with staff time was calculated using the mid-point of the HSE salary scales and adjusted for non-pay salary costs as per the guidelines [384, 385]. Unit cost data for all laboratory and diagnostic tests were obtained from the laboratory and finance departments of the relevant hospitals. The 2013 Casemix Ready Reckoner provided DRG costs used for the costing of hospital inpatient admissions [383]. Unit drug costs were taken from the HSE Primary Care Reimbursement Service (PCRS) and were calculated using the NCPE guidelines for inclusion of drug costs in pharmacoeconomic evaluations [386, 387]. All on-treatment costs

were adjusted to June 2015 levels and post-SVR costs and post-discontinuation costs adjusted to April 2016 levels using the Central Statistics Office Consumer Price Index [388].

6.3 Statistical Analysis

Descriptive statistics were performed on the results to give mean values with 95% confidence intervals (CI). Although the data from our sample was skewed, the mean cost was determined instead of the median cost as this data is more relevant to the entire population, not just the cohort sampled in this analysis. The 95% CI were estimated by non-parametric bootstrapping to account for the skewed nature of cost distributions. A Mann Whitney U test was performed to assess the differences in cost outcomes between subgroups of patients treated with IFN-based and IFN-free regimens and subgroups of patients with or without cirrhosis. In the post-SVR and post-discontinuation sub-study, patient-level data was obtained from the study by Kieran *et al* in order to compare the mean annual costs of untreated HCV versus post-treatment expenditure [81]. A *p*-value less than 0.05 were considered statistically significant. The analysis was performed using Microsoft Excel Version 14.6 (Microsoft Corporation, Redmond, Washington, USA) and SPSS Version 21® (IBM Corp, Armonk, NY, USA).

6.4 Results - Sub-study 1

The mean on-treatment costs for IFN-based regimens were based on a sample of 119 patients with GT1 HCV infection treated with BOC/PR (n=40) or TPV/PR (n=79). Patients with and without cirrhosis were included in the analysis. Duration of treatment was determined by baseline patient characteristics and/or in accordance with recommended stopping rules dependent on the on-treatment virological response.

The mean on-treatment costs of IFN-free regimens were based on a sample of 47 patients treated with SOF/LDV±RBV (n=35) or 3D±RBV (n=12). Cirrhotic patients with both GT1 or GT3 HCV infection with a CTP score of B or C, and/or a prior episode of decompensation i.e. advanced liver disease, were treated with SOF/LDV±RBV for 12 weeks. Cirrhotic patients with GT1 or GT4 with mild cirrhosis (CTP A) were treated with 3D±RBV (GT1 or GT4) for 12 or 24 weeks depending on GT1 subtype. A total of 3 patients with GT1a received 24 weeks of therapy.

6.4.1 Patient Demographics

Of those treated with IFN-based regimens, 69% (n=82/119) were male, with a median age of 46 years (IQR 37-56). Patients previously treated with PR accounted for two-thirds of the cohort (64%), while 35% were cirrhotic (Table 24). The SVR rate within this cohort was 61% (n=73/119), 49% in cirrhotic patients and 70% in those without cirrhosis. The mean treatment duration was 30 weeks. Seventy-three patients (61%) completed a full treatment course. Forty-six patients discontinued treatment prematurely, with treatment duration ranging from 1 to 39 weeks.

In the IFN-free cohort, thirty-three patients were male (70%) and the median age was 50 years (IQR 42-56). Of this cirrhotic cohort, twelve were classified as CTP A, twenty-four CTP B and eleven CTP C. Seventeen patients (36%) had previously received treatment for HCV infection (Table 24). The SVR rate was 68% (n=32/47). The mean treatment duration was 12.3 weeks. Thirty-nine patients (83%) completed full treatment courses. Eight patients discontinued treatment prematurely, with treatment duration ranging from 3 to 18 weeks.

Table 24: Baseline demographic profile of n=166 patients

	Total Cohort n=166	IFN-based n=119	IFN-free n=47	*P*-value
Male, n (%)	115 (69)	82 (69)	33 (70)	0.871
Median Age (IQR)	47 (39-56)	46 (37-56)	50 (42-56)	0.796
Treatment Experienced, n (%)	93 (56)	76 (64)	17 (36)	0.001
Cirrhotic, n (%)	88 (54)	41 (35)	47 (100)	<0.001
Genotype, n (%)				
GT1	43 (26)	27 (22)	16 (34)	0.393
GT1a	73 (44)	56 (47)	15 (32)	
GT1b	37 (22)	34 (29)	3 (6)	
GT3	8 (5)	-	8 (17)	
Other	5 (3)	2 (2)	5 (11)	

6.4.2 Direct Treatment Costs for Interferon-based Regimens

The overall cost of the cohort treated with IFN-based regimens was €4,556,039. HCV drug acquisition costs represented the largest component of the overall cost, contributing 85% (€3,856,802) of the total expenditure. On-treatment costs associated with patient monitoring, treatment of AEs, and inpatient admissions (henceforth described as “treatment management costs”) accounted for €699,416 with a mean of €5,877 (95% CI €5,161-€6,675) per patient. The mean cost of treatment per patient was €38,286 (95% CI €35,305-€41,061). The mean cost per SVR was €62,457.

6.4.3 Treatment Management Costs for Interferon-based Regimens

The mean monitoring costs (laboratory investigations, diagnostic investigations and HCV-PCR assays) per patient was €2,111 (95% CI €1,938 - €2,273), ranging from €65 to €5,108. The mean cost of AE management per patient was €1,811 (95% CI €1,208 - €2,465). Interventions for the management of anaemia, neutropenia and thrombocytopenia were the most costly (€187,149) and contributed to 93% of the total spending on AEs. The most common reasons for admissions were drug-induced AEs. Length of hospital stay ranged from 1 to 14 days. Results are summarised in Table 25.

Table 25: Components of treatment management costs - IFN-based treatment regimens

Resource	Cost	Proportion of treatment management costs	Mean cost per patient (95% CI)
On-treatment monitoring costs			
Laboratory Investigations	€159,746	23%	€1,342 (€1,230- €1,469)
Diagnostic Investigations	€28,329	4%	€238 (€186- €300)
HCV-PCR Assays	€63,115	9%	€530 (€491- €571)
On-treatment AE management costs			
Medicines for AEs (including blood transfusions)	€200,421	29%	€1,683 (€1,152- €2,345)
Referrals (to other hospital clinical services)	€15,255	2%	€128 (€91– €178)
Admissions	€28,335	4%	€238 (€97- €406)
OPD staff costs	€131,903	19%	€1,108 (€1,011- €1,207)
Baseline work-up	€72,312	10%	€608*
Total Expenditure	€699,416		€5,877 (€5,161 – €6,675)

AE=adverse events, HCV = hepatitis C, PCR = polymerase chain reaction, OPD = outpatient department, CI = confidence interval
* Estimated cost

6.4.4 Direct Treatment Costs for Interferon-free Regimens

The total cost of treating the IFN-free cohort was €2,619,946. HCV drug costs accounted for the largest component of the overall costs, contributing 89% (€2,339,725) of total expenditure. Treatment management costs accounted for €279,620 of the total expenditure representing a mean cost of €5,950 (95% CI €4,359 - €7,959) per patient. The mean cost of treatment per patient was €55,734 (95% CI €50,906 - €60,880). The mean cost per SVR was €81,873.

6.4.5 Treatment Management Costs for Interferon-free Regimens

The mean monitoring cost per patient was €2,210 (95% CI €1,979 - €2,460), ranging from €140 to €4,176. The mean cost of AE management per patient was €365 (95% CI €244 - €497). In total, eleven patients required admission. Nine patients were admitted for reasons related to disease progression (ascites, variceal bleeds, hepatic encephalopathy and decompensation). The remaining two patients were admitted for treatment of drug-induced AEs. Length of hospital stay ranged from 1 to 84 days. The total expenditure on the eleven admissions was €93,859. The nine admissions that

were related to disease progression amounted to €88,247. Results are summarised in Table 26.

Table 26: Components of treatment management costs - IFN-free treatment regimens

Resource	Cost	Proportion of treatment management costs	Mean cost per patient (95% CI)
On-treatment monitoring costs			
Laboratory investigations	€53,492	19%	€ 1,138 (€970-€1,299)
Diagnostic investigations	€13,311	5%	€283 (€222-€348)
HCV-PCR Assays	€36,479	13%	€777 (€696-€855)
On-treatment AE management costs			
Medicines for AEs (including blood transfusions)	€10,413	4%	€222 (€114-€348)
Referrals (to other hospital clinical services)	€6,760	2%	€144 (€82-€218)
Admissions	€93,859	34%	€1,997 (€476-€4,036)
OPD staff costs	€33,153	12%	€705 (€632-€780)
Baseline Work-Up	€32,153	11%	€684[#]
Total Expenditure	€279,620		€5,950 (€4,359 - €7,959)

AE=adverse events, HCV = hepatitis C, PCR = polymerase chain reaction, OPD = outpatient department, CI = confidence interval
* Estimated cost

6.4.6 Comparison of the Treatment Monitoring Costs Between the Interferon-based and Interferon free Regimens

Figure 35 compares the proportion that each resource contributed to the treatment monitoring costs between the IFN-based and IFN-free cohorts. In the IFN-based cohort, laboratory investigations (23%) and medicines for the management of AEs (29%) were the largest contributors to these treatment management costs. In the IFN-free cohort, admissions (34%) accounted for the largest component of these costs followed by the laboratory investigations.

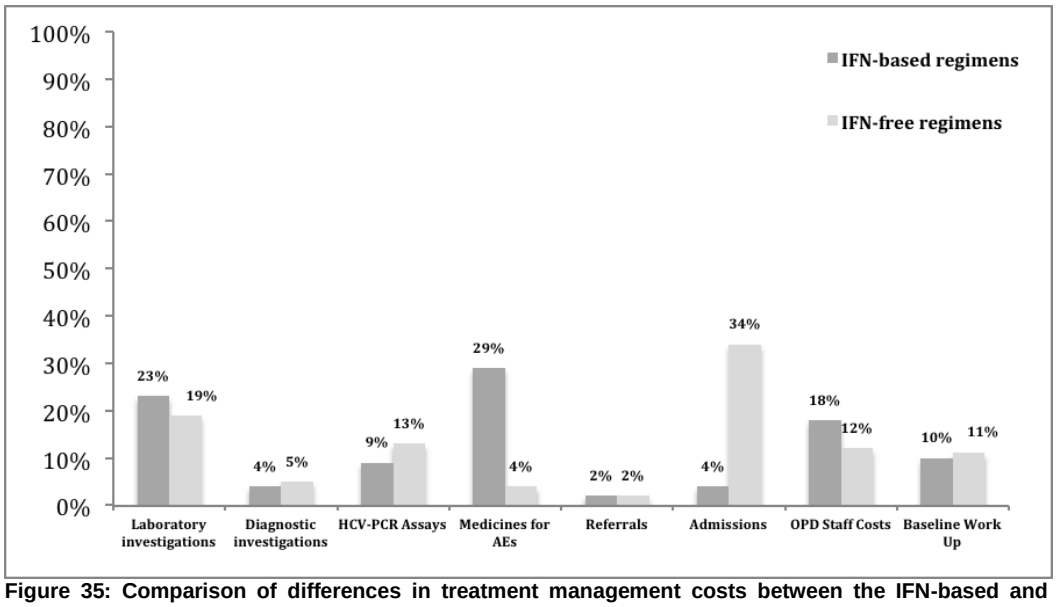


Figure 35: Comparison of differences in treatment management costs between the IFN-based and IFN-free regimens

A Mann Whitney U test was performed to examine for a difference in costs between the IFN-based and IFN-free treatments and results are presented in Table 27. The mean cost per patient (p = 0.001) and the cost of HCV-PCR assays (p = 0.001) were statistically significantly higher in the IFN-free regimens whereas the mean cost of the management of AEs (p = 0.005) and the cost of staff (p = 0.001) were statistically significantly higher in the IFN-based regimens.

Table 27: Differences in costs between the IFN-based and IFN-free cohorts

		Total Costs; Mean	Total Costs; Mean Difference (95% CI)	P-Value
Total Costs per Patient	IFN-free	€55,744	€17,458	0.001*
	IFN-based	€38,286	(€12,092 - €23,177)	
Treatment Management Costs per Patient	IFN-free	€5,962	€86	0.937
	IFN-based	€5,876	((-€1,594) - €2,237)	
On-treatment Monitoring Costs per Patient	IFN-free	€2,210	€99	0.536
	IFN-based	€2,111	((-€210)- €407)	
AE-management Costs per Patient	IFN-free	€365	-€1,446	0.005*
	IFN-based	€1,811	(€871- €2,119)	
Laboratory Costs per Patient	IFN-free	€1,144	-€198	0.059
	IFN-based	€1,342	((-€13)- €394)	
HCV-PCR Assay Costs per Patient	IFN-free	€783	€253	0.001*
	IFN-based	€530	(€164 - €341)	
Diagnostic Costs per Patient	IFN-free	€283	€45	0.293
	IFN-based	€238	((-€36)- €136)	
Referral Costs per Patient	IFN-free	€144	€16	0.708
	IFN-based	€128	((-€61) - €104)	
Admission Costs per Patient	IFN-free	€1,997	€1,759	0.208
	IFN-based	€238	(€274- €3,944)	
Staff Costs per Patient	IFN-free	€705	-€403	0.001*
	IFN-based	€1,108	(€276 - €531)	

6.4.7 Comparison of the Treatment Management Costs between Cirrhotic Patients in the Interferon-based and Interferon-free Cohorts

A total of forty-one patients with cirrhosis were included in the cohort treated with IFN-based regimens of whom 49% (n=20/41) obtained a SVR24. The total costs for treating these patients was €1,603,821 resulting in a cost per SVR of €80,191 compared to a mean cost per SVR of €81,873 for the cohort treated with IFN-free regimens. We examined for a difference in costs between patients with cirrhosis in the two cohorts. While the costs for many of the components were very similar, statistically significant differences were observed in four categories (Table 28).

Table 28: Statistically significant differences in costs between the cirrhotic IFN-based and IFN-free cohorts

		Total Costs; Mean	Total Costs; Mean Difference (95% CI)	P-Value
Total Costs per Patient	IFN-free	€55,744	€16,626	0.001*
	IFN-based	€39,118	(€9,451 - €24255)	
AE-management Costs per Patient	IFN-free	€365	-€1,791	0.004*
	IFN-based	€2,156	(€993- €2,735)	
HCV-PCR Assay Costs per Patient	IFN-free	€783	€255	0.001*
	IFN-based	€528	(€152 - €348)	
Staff Costs per Patient	IFN-free	€705	-€587	0.001*
	IFN-based	€1,292	(€367 - €805)	

6.4.8 Sensitivity Analysis: Comparison of Treatment Management Costs Between the Interferon-based and Interferon-free Cohorts Excluding the Costs of Admissions for Disease Progression

With nine out of eleven admissions in the IFN-free cohort attributed to disease progression (calculated costs of €88,247), the comparative analysis was repeated to determine the impact of excluding these admissions on treatment costs as we expect the HCV-related admissions to fall as treatment is extended to those with milder liver disease. This resulted in a reduction in the mean treatment costs per patient for the IFN-free regimens (from €55,744 to €53,866), the mean treatment management costs (from €5,962 to €4,084) and the mean cost of admission (from €1,997 to €119) per patient by €1,878 (Table 29).

Table 29: Changes in treatment management costs following the exclusion of admission related to disease progression

		Total Costs; Mean (excluding admissions related to disease progression)	Total Costs; Mean (including all admissions)	Difference
Total Costs per Patient	IFN-free	€53,866	€55,744	€1,878
	IFN-based	€38,268	€38,286	€0
Treatment Management Costs per Patient	IFN-free	€4,084	€5,962	€1,878
	IFN-based	€5,876	€5,876	€0
Admission Costs per Patient	IFN-free	€119	€1,997	€1,878
	IFN-based	€238	€238	€0

Figure 36 compares the proportion of resources contributing to the treatment management costs between the IFN-based and IFN-free cohorts in this scenario.

Laboratory investigations (28%) become the largest contributor to the treatment management costs in the IFN-free cohort followed by HCV-PCR assays (19%).

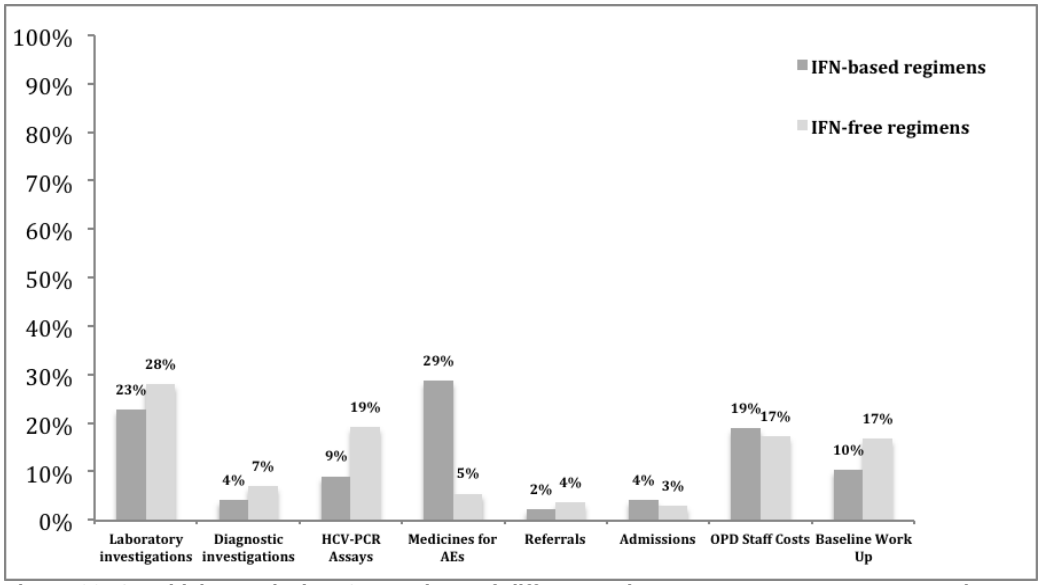


Figure 36: Sensitivity Analysis - Comparison of differences in treatment management costs between the IFN-based and IFN-free regimens

This compares the differences in treatment management costs following the exclusion of the cost of admissions for disease progression. Laboratory investigation costs become the largest contributor to the IFN-free-related treatment management costs

6.5 Discussion – Sub-study 1

This study reports real world DAA treatment costs in the Irish setting for both IFN-based and IFN-free regimens. To our knowledge, prior to publication of these data, there was no published literature on the direct costs of treatment with IFN-free regimens and this was the first study to compare the costs between the two regimens.

The results from the IFN-based cohort were compared with a number of published studies. Thorlund *et al* estimated a cost per SVR for TPV/PR of $74,380-$76,370 (€65,632-€67,388), calculated using clinical trial data with SVR24 rates of 70%-90% whereas a SVR24 rate of 61% was obtained in this study sample [389]. Although our real world study had a lower SVR24 rate, the result from Thorlund *et al* is comparable with the cost per SVR estimated from our study. Bichoupan *et al* estimated a cost per SVR

for TPV/PR of $189,338 (€167,221) [376], while a recent real world study published in 2015 by Sethi *et al* reported a cost per SVR of $172,889 (€152,718) and a mean cost per patient of $83,851 (€74,056) in patients treated with first-generation DAAs in combination with PR [375]. The costs from the latter two studies are significantly higher than the estimate from this study and from Thorlund *et al*. Further investigation identified that a SVR24 rate of 44%-45% in these two studies was the driver of the higher cost per SVR. This highlights the impact of using real world versus clinical trial data for determining treatment costs.

In the IFN-free cohort (100% cirrhosis), the cost per SVR was €81,873. The difference between this and the cost per SVR in the IFN-based group (35% cirrhosis) (€62,457) was driven by the difference in cost of HCV medication. It is important to note that the cost per SVR in the IFN-free cohort was based on a cohort of patients with advanced liver disease and a SVR12 rate of 68% (n=47). As this treatment is extended to patients with milder liver disease, the SVR12 rate is expected to increase, (as evident by the improved SVR12 rate in our cohort of patients with compensated cirrhosis presented in *Chapter 5*) thus reducing the cost per SVR for IFN-free therapies. An increase in SVR rate to 80%‡ would reduce the cost per SVR to €70,809 based on the costs accrued in this IFN-free study.

For both the IFN-based and IFN-free regimens, HCV medication costs are by far the largest contributor to the total costs. The proportion to which the treatment management costs (on-treatment costs associated with patient monitoring, treatment of AEs, and inpatient admissions) contribute to the total treatment costs is lower in the

‡ An 80% SVR rate was chosen as an example since the effectiveness in a real world cohort is often lower than RCTs. While the SVR rate for this IFN-free cohort was 68%, these were patients with advanced liver disease. As patients with less advanced disease, and lower clinical priority are treated, the SVR rate would be expected to increase.

IFN-free cohort (15% in IFN-based vs. 11% in IFN-free regimens). Additionally, there are key differences between each cohort in terms of the resources that drive these costs. In the IFN-based cohort, medication for the management of AEs was the most costly component of the treatment management costs. Although, the IFN backbone and the two first generation protease inhibitors TPV and BOC were associated with significant side effects, these were well managed in the outpatient clinics and few inpatient admissions were required. In contrast to this, the cost of inpatient admission was the largest component of the treatment management costs for those treated with IFN-free regimens. While the absence of the IFN-backbone should have resulted in fewer adverse events, the advanced nature of the disease in patients treated with these IFN-free regimens resulted in a large number of admissions for the treatment of hepatic encephalopathy and ascites associated with disease progression (and not associated with treatment side effects). Of the eleven patients in the IFN-free cohort admitted during treatment, nine were admitted as a result of disease progression (ascites, variceal bleeds, hepatic encephalopathy and decompensation). These contributed €88,247 to the total cost of admission, while the remaining €5,612 was as a direct result of treatment-related AEs. Excluding the cost of disease progression-related admissions in the analysis resulted in a reduction in the treatment managements costs. Consequently, we can predict that as patients with mild liver disease receive treatment with these regimens, the contribution of the cost of inpatient admissions to the overall costs will reduce and will likely fall below the equivalent costs reported with the IFN-based regimens.

A recently published study to determine the real world costs of untreated HCV in Ireland discussed the contribution of AE management to the overall cost of treatment with PR (pre-DAA era) for HCV infection [81]. The authors hypothesised that, given the improved side effect profile, the treatment costs would reduce with the introduction of

the IFN-free regimens, which has now been demonstrated in this study. However, in this study the cost of AE management has been superseded by the cost of therapy and the cost of on-treatment admissions. Given that this IFN-free cohort were prioritised for treatment on the basis of clinical need, the expected reduction in patients requiring admission (and the costs associated with those admissions) when the availability of IFN-free regimens are extended to patients with mild liver disease (absence of cirrhosis) should lead to an improved SVR12 rate and an improved cost per SVR12.

The cost per SVR24 in patients with cirrhosis in the IFN-based cohort was similar to the cost per SVR obtained in the IFN-free cohort (€80,191 vs. €81,873). This can be explained by the difference in SVR12/24 rates observed in the two cirrhotic cohorts (49% in IFN-based regimens vs. 68% in IFN-free regimens). As patients with less advanced disease begin to receive treatment with the IFN-free regimens, the SVR12 rate is expected to increase. Thus, it would be reasonable to expect that the cost per SVR would be lower in a non-cirrhotic cohort.

6.6 Results - Sub-study 2

A total of 110 patients were eligible for inclusion in this study. This included a sample of 67 patients who had achieved a SVR24 following treatment with the IFN-based regimens and a further 43 patients who had achieved a SVR12 following treatment with the IFN-free regimens.

6.6.1 Patient Demographics

The baseline demographic profile of the patients included in this study is presented in Table 30**.** The overall cohort was predominantly male (76%) and cirrhosis was present in 51%. Of those treated with IFN-based regimens, 49 (73%) were male, with a median

age of 42 years (IQR 31-65). Patients previously treated with PR accounted for 54% of this cohort (n=36/67), while 19% were cirrhotic. In the IFN-free cohort, 34 patients were male (79%) and the median age was 53 years (IQR 45-61). All patients treated with the IFN-free regimens had cirrhosis, with nineteen classified as CTP A, twenty CTP B and four CTP C. Twenty-one patients (n=21/43, 49%) had previously received treatment for HCV infection. There were statistically significant differences observed in selected characteristics including age, presence of cirrhosis and present or previous history of decompensation (p<0.001) between the two groups.

Table 30: Baseline demographic profile of n=110

	Total Cohort n=110	**IFN-based n=67**	**IFN-free n=43**	***P*-value**
Male, n (%)	83 (76)	49 (73)	34 (79)	0.485
Median Age (IQR)	46 (39-56)	42 (35-51)	53 (45-61)	<0.001
Treatment Experienced, n (%)	57 (51)	36 (54)	21 (49)	0.707
Cirrhotic, n (%)	56 (51)	13 (19)	43 (100)	<0.001
Genotype, n (%)				
GT1	23 (19)	8 (12)	15 (35)	0.395
GT1a	67 (63)	46 (69)	21 (49)	
GT1b	17 (15)	13 (19)	4 (9)	
GT3	2 (2)	-	2 (5)	
GT4	1 (1)	-	1 (2)	
CTP Score*, n (%)				
A	32 (29)	13 (19)	19 (44)	N/A
B	20 (18)	N/A	20 (47)	
C	4 (4)	N/A	4 (9)	
Decompensation, n (%)	8 (7)	-	8 (19)	

CTP = Child's Turcotte Pugh, GT = Genotype, N/A = Not available
*Relevant for cirrhotic patients only

6.6.2 Resource Utilisation in the Post-SVR Period

In the 12-month period following achievement of a SVR24, patients treated with IFN-based regimens, returned for an outpatient clinical assessment an average of 2.7 times (95% CI 2-3.5). During these visits, the patient was seen by a consultant grade physician or doctor-in-training on average 1.2 occasions (95% CI 1-1.4) or by a CNS 1.5 times (95% CI 0.9-2.3). The mean number of blood samples taken per patient per year, for laboratory investigations, was 1.8 (95% CI 1.3-2.5) and patients underwent

HCV-PCR assays 1.3 times (95% CI 1.1-1.5) in the 12-month period following SVR24. Diagnostic investigations and referral to other hospital services were infrequent. A liver ultrasound was the most commonly utilised diagnostic procedure (0.4 times per patient) during this post-SVR period (Table 31**).**

In the 12-month period post-SVR12, patients treated with IFN-free regimens attended for an outpatient clinical assessment on average 6.9 times (95% CI 5.8-8.2). During these visits, patients were assessed by a physician (consultant grade or doctor-in-training) on 2.6 occasions (95% CI 1.8-3.6) or by a CNS on 4.3 occasions (95% CI 3.2-5). Laboratory investigations were completed approximately every 2 months (5.4 times per patient, per year) while HCV-PCR assays were undertaken 3.2 times (95% CI 2.7-3.6). The average number of liver ultrasounds completed in the 12-month period was 1.1 per patient (95% CI 0.8-1.4) while referrals to other hospital services were uncommon (Table 31).

The Mann Whitney U test determined that statistically significant differences were observed in the mean annual resource utilisation between patients treated with IFN-based and IFN-free regimens. These results were expected given that the IFN-free cohort consisted exclusively of patients with cirrhosis, whereas presence of cirrhosis was limited to 19% of the IFN-based cohort and therefore, were likely to utilise less resources following SVR24.

Table 31: Resources utilised by patients during the post-SVR12/24 period

	IFN-based regimens (n=67)	**IFN-free regimens (n=43)**	***P*-value**
OPD Visit	2.7 (95% CI 2-3.5)	6.9 (95% CI 5.8-8.2)	<0.001
Laboratory Investigations	1.8 (95% CI 1.3-2.5)	5.4 (95% CI 4.5-6.5)	<0.001
HCV-PCR Assay	1.3 (95% CI 1.1-1.5)	3.2 (95% CI 2.5-3.7)	<0.001
Liver U/S	0.4 (95% CI 0.2-0.6)	1.1 (95% CI 0.8-1.4)	0.007
Referral	0	0.7 (95% CI 0.3-1.2)	0.033
Admissions (Inpatient days)	0.02 (95% CI 0-0.06)	6.8 (95% CI 1.4-25.9)	0.087

6.6.3 Mean Annual Healthcare Costs in the Post-SVR Period

The mean annual ambulatory care expenditure by a patient treated with IFN-based regimens following a SVR24 was €500 (95% CI €390-€631). Laboratory investigations (blood tests such as a full blood count, thyroid function tests, liver and renal profile etc.) were the greatest contributor to these costs, with an average expenditure of €246 per patient (95% CI €171-€330) (Figure 37). This was followed by HCV-PCR assays and diagnostic procedures, accruing mean annual costs of €114 and €75 per patient, respectively, post-SVR (Table 32).

Following achievement of a SVR12, the mean annual cost of HCV care for patients treated with IFN-free regimens was €2,808 (95% CI €1,468-€4,961). Inpatient admissions were the largest component of these costs (€1,565 (95% CI €288-€3,672)), followed by laboratory investigations (€411 (95% CI €334-€497) and diagnostic procedures (€304 (95% CI €213-€488)) of which liver ultrasounds contributed a mean annual cost of €157 (95% CI €108-€199) (Figure 37).

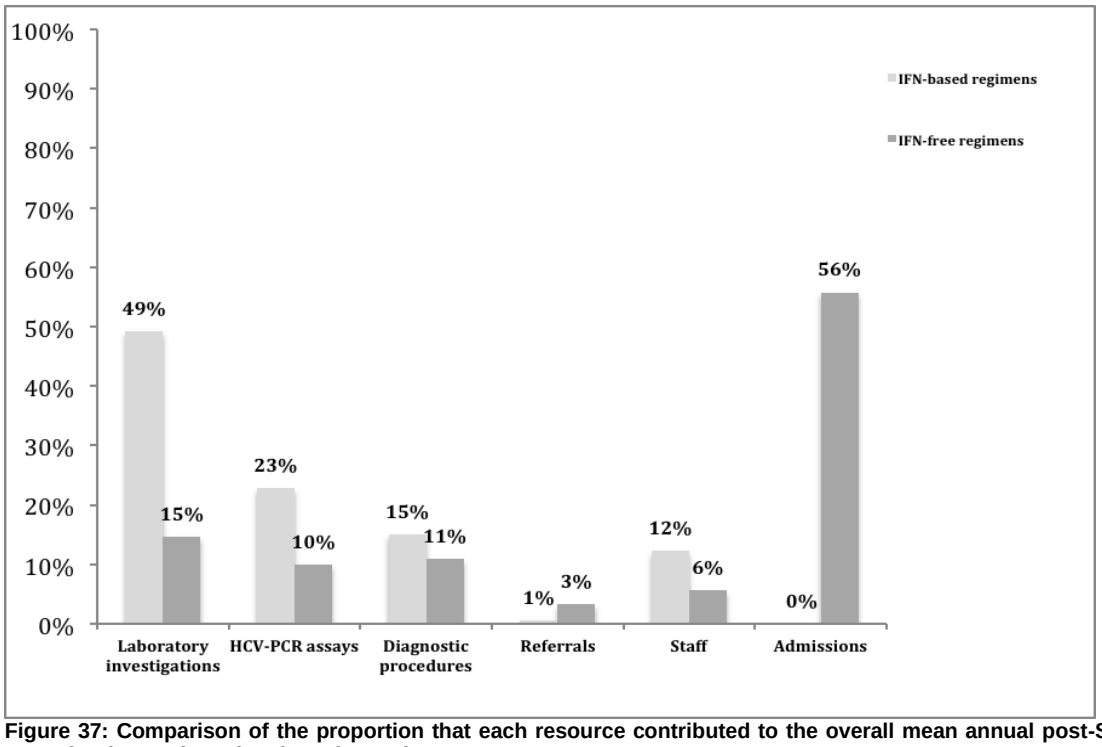


Figure 37: Comparison of the proportion that each resource contributed to the overall mean annual post-SVR costs for the IFN-based and IFN-free cohorts

After examining for a difference in resource utilisation between the IFN-based and IFN-free treatments, a statistically significant difference in mean annual costs, for all categories of expenditure with the exception of admissions, following SVR12 or SVR24, was identified. The mean annual costs were higher in patients treated with IFN-free regimens compared to those treated with IFN-based regimens (Table 32).

Table 32: Costs accrued by patients during the post-SVR12/24 period

	IFN-based regimens	IFN-free regimens	*P*-value
Laboratory Investigations	€246 (95% CI €171-€330)	€411 (95% CI €334-€497)	0.0011
HCV-PCR Assays	€114 (95% CI €94-€136)	€280 (95% CI €240-€319)	<0.001
Diagnostic procedures	€75 (95% CI €50-€103)	€304 (95% CI €213-€488)	0.001
Referrals	€3 (95% CI €0-€10)	€91 (95% CI €42-€148)	0.003
Staff	€61 (95% CI €46-€78)	€157 (95% CI €130-€187)	<0.001
Admissions	€0	€1,565 (95% CI €288-€3672)	0.097
Total	€500 (95% CI €390-€631)	€2,808 (95% CI €1468-€4961)	0.017

6.6.4 Admissions

The number of bed days and subsequent cost of liver-related admissions were included in the analysis of the total costs. No patients in the IFN-based cohort were admitted during the post-SVR period for liver-related events.

In those who received treatment with IFN-free regimens, seven patients were admitted to hospital with an average length of stay of 21 days (range 3-76 days). Three of these patients had prior history of decompensation, five were CTP B, one was CTP A while the remaining patient was CTP C. Two patients were admitted for the treatment of varices and four patients were admitted with hepatic encephalopathy and liver decompensation. Two of these patients died during their admission period. The remaining patient was admitted for psychiatric care. The average cost of hospital admission for these seven patients was €9,612 (range €1,215-€37,468). When applied across the cohort, the mean annual cost of admissions per patient was €1,565 (95% CI €288-€3,672).

6.6.5 Comparison of the Mean Annual Costs in Patients With and Without Cirrhosis

After stratifying the cohort according to the presence or absence of cirrhosis, we examined for differences in mean annual costs between the two subgroups, irrespective of treatment regimen. There was a statistically significant difference in the overall mean annual post-SVR cost between patients with cirrhosis and without cirrhosis and for each component of these total costs (Table 33).

Table 33: Comparison of the costs in all patients, stratified according to the presence or absence of cirrhosis

	With cirrhosis n=56	Without cirrhosis n=54	*P*-value
Laboratory Investigations	€377 (95% CI €304-€462)	€242 (95% CI €151-€346)	0.033
HCV-PCR Assays	€235 (95% CI €200-€278)	€120 (95% CI €98-€144)	<0.001
Diagnostic procedures	€261 (95% CI €186-€426)	€66 (95% CI €38-€97)	<0.001
Referrals	€70 (95% CI €33-€116)	€4 (95% CI €0-€12)	0.004
Staff	€132 (95% CI €111-€161)	€64 (95% CI €46-€87)	<0.001
Admissions	€1,201 (95% CI €191-€2851)	€0 (95% CI €0-€30)	0.001
Total	€2,276 (95% CI €1258-€3993)	€495 (95% CI €388-€659)	0.017

6.6.6 Comparison of the Mean Annual Costs Between Untreated HCV and Post-SVR Individuals

The post-SVR costs obtained in this study, irrespective of treatment regimen, were stratified by disease severity and were compared with the mean annual medical costs of untreated HCV reported by Kieran *et al* [81]. The most significant difference observed between the mean annual untreated HCV costs and mean annual post-SVR costs was in those individuals with decompensated cirrhosis, where a reduction in the mean annual costs of €4,369 was observed following SVR12 (*p*-value = 0.044). The post-SVR costs in individuals with F0-F3 fibrosis (mild to moderate disease) were higher than the mean annual costs of untreated HCV for individuals with mild and moderate disease, as reported by Kieran *et al* [81]. In individuals with compensated cirrhosis, the mean annual post-SVR costs were higher than the mean annual costs for untreated HCV with a mean difference of €528 but this was not considered statistically significant (p-value = 0.670) (Table 34).

Table 34: Comparison between the mean annual costs for untreated HCV and the mean annual costs following SVR stratified by severity of liver disease

	Mean annual costs for untreated HCV (Kieran *et al)*	Mean annual post-SVR costs	Mean Difference	*P*-Value
F0-F3	€404 (95% CI €354-€458)	€505 (95% CI €378-€661)	€101	0.193
Compensated cirrhosis	€1,762 (95% CI €974-€3229)	€2,290 (95% CI €1156-€4239)	€528	0.670
Decompensated cirrhosis	€6,564 (95% CI €4481-€9423)	€2,195 (95% CI €572-€5055)	-€4,369	0.044

Given that patients with compensated cirrhosis (n=48) were treated with either IFN-based (n=13) or IFN-free (n=35) regimens, we reassessed the mean annual post-SVR costs, stratifying according to treatment with or without IFN. This demonstrated that post-SVR expenditure in patients treated with IFN-free regimens was €2,427 (*p*-value = 0.192) greater than the post-SVR expenditure following treatment with IFN-based regimens in patients with compensated cirrhosis (Table 35). Additionally, it established that the mean annual post-SVR costs in patient with compensated cirrhosis treated with IFN-based regimens (€521) was lower than the mean annual costs for untreated HCV in compensated cirrhosis (€1,762). The mean annual post-SVR costs in patients with compensated cirrhosis treated with IFN-free regimens (€2,948) was higher.

Table 35: The mean annual post-SVR costs in patients with compensated cirrhosis stratified according to treatment regimen.

	Mean annual post-SVR costs following IFN-based treatment	Mean annual post-SVR costs following IFN-free treatment	Mean Difference	*P*-Value
Compensated cirrhosis	€521 (95% CI €308-€764)	€2,948 (95% CI €1391-€5484)	€2,427	0.192

A closer examination of the resource utilisation and expenditure within this sub-group of patients with compensated cirrhosis was undertaken. Statistically significantly differences in resource utilisation and expenditure was observed in patients with compensated cirrhosis stratified according to treatment regimen (Table 36).

Table 36: Post-SVR resource utilisation and expenditure in patients with compensated cirrhosis stratified according to treatment regimen

	IFN-based regimens n=13	IFN-free regimens n=35	*P*-value
OPD Visits (n)	2.2 (95% CI 1.3-3.3)	7.5 (95% CI 6.3-8.8)	<0.001
HCV-PCR Assays (n)	1 (95% CI 0.5-1.7)	3.3 (95% CI 2.8-3.8)	<0.001
Laboratory Investigations	€265 (95% CI €103-€486)	€433 (95% CI €342-€547)	0.108
HCV-PCR Assays	€89 (95% CI €44-€149)	€293 (95% CI €249-€339)	<0.001
Diagnostic procedures	€116 (95% CI €63-€179)	€372 (95% CI €245-€523)	0.002
Referrals	€0	€104 (95% CI €48-€201)	0.003
Staff	€49 (95% CI €29-€75)	€170 (95% CI €142-€201)	<0.001
Admissions	€0	€1,575 (95% CI €100-€3973)	0.387

6.6.7 Sensitivity Analysis

Given that, out of ninety-four patients, eight patients were admitted for liver-related admissions, a sensitivity analysis was completed to determine the impact of excluding the cost of these inpatient admissions on overall costs as we would expect liver-related admissions to decrease as patients with milder disease are treated.

Figure 38 demonstrates that, when the cost of inpatient admissions following SVR are excluded, the proportion that each resource contributed to the total costs changed significantly in the IFN-free cohort. The largest driver of post-SVR costs for both cohorts was laboratory investigations (49% and 32% (p<0.001) for IFN-based and IFN-free cohorts, respectively). A statistically significant difference was observed in the proportion of expenditure on diagnostic procedures in the IFN-free regimens compared to the IFN-based regimens (p=<0.05). Further results are presented in Appendix 3 Table A12 - Table A14. The most important difference is that, in the absence of inpatient admissions, the mean annual post-SVR costs in patient with compensated cirrhosis treated with IFN-free regimens is lower, by €171, than the mean annual costs of untreated HCV in patients with compensated cirrhosis (Appendix 3 Table A14). This contrasts with the significantly higher post-SVR costs that were observed when the cost of inpatient admissions were included in the analysis.

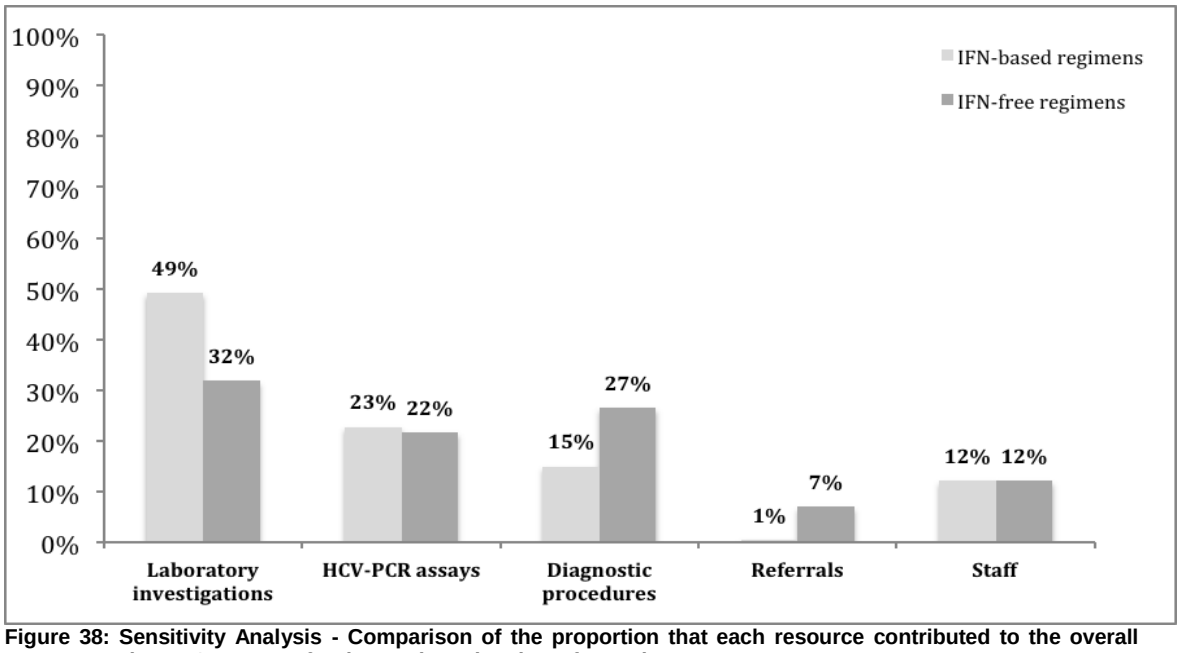


Figure 38: Sensitivity Analysis - Comparison of the proportion that each resource contributed to the overall mean annual post-SVR costs for the IFN-based and IFN-free cohorts

The sensitivity analysis reassessed the proportion that each resource contributed to the overall mean annual post-SVR costs following exclusion of the cost of inpatient admissions

6.7 Discussion – Sub-study 2

The contrast observed in the baseline HCV characteristics between patients treated with the IFN-based and IFN-free regimen can account for the statistically significant differences in the utilisation of ambulatory care resources and subsequent expenditure in the post-SVR period.

Given that treatment with IFN-based regimens was associated with a number of additional factors including challenging side effect profiles, many patients with advanced cirrhosis were withheld from treatment as a result of the findings from a study by Hezode *et al* [157]. This study reported that, in cirrhotic patients exposed to protease inhibitor triple therapy (i.e. TPV/PR or BOC/PR) regimens, albumin levels <35 g/L and platelet count ≤100,000m^3 were independent predictors of death and severe complications. Thus, with the introduction of the IFN-free regimens in late 2014, patients whom had been withheld from IFN-based DAA treatment and now deemed in greatest clinical need, those with decompensated cirrhosis or compensated cirrhosis

and at risk of irreversible liver damage or death, were prioritised for treatment. However, although the IFN-free cohort consisted exclusively of patients with cirrhosis, the statistically significantly greater resource utilisation and expenditure in the post-SVR period was unexpected and requires further investigation.

In this study, the mean annual post-SVR ambulatory care expenditure was higher in the IFN-free cohort than the IFN-based cohort. The continued assessment of HCV-RNA after confirmation of SVR is notable. Given the significant amount that these assays contribute to the mean annual post-SVR costs, investigation into the driver of these repeated assays is necessary. It is possible that there was a clinical concern with re-infection or delayed virological relapse that required monitoring. As clinician familiarity and confidence in the durability of the SVR12 achieved using IFN-free regimens grows, it is likely that this level of HCV testing will decrease.

The results obtained in this study enabled us to make a comparison between the costs of untreated HCV and the costs accumulated during the post-SVR period for patients without cirrhosis, with compensated cirrhosis and with decompensated cirrhosis. We compared our post-SVR costs with the mean annual costs of untreated HCV reported in a study by Kieran *et al* in 2015 [81]. This enabled the identification of the benefits of successful treatment. The most significant difference was observed in patients with decompensated cirrhosis. Following a SVR12, the healthcare costs were statistically significantly lower (by €4,369) than the healthcare costs in untreated HCV-infected patients with decompensated cirrhosis. However, increases in expenditure post-SVR were observed in patients without cirrhosis (F0-F3) and in patients with compensated cirrhosis. A more detailed analysis of the cohort with compensated cirrhosis identified that the post-SVR costs in patients treated with IFN-based regimens was lower than the cost of untreated HCV in patients with compensated cirrhosis, however, those treated with IFN-free regimens had a greater expenditure in the post-SVR period than

in untreated HCV, largely attributable to the cost of inpatient admissions in these patients. We noted statistically significantly higher resource utilisation and expenditure in patients with compensated cirrhosis treated with IFN-free regimens when compared with those treated with IFN-based regimens. However, the intensity of patient assessments would be anticipated to fall as clinicians become more familiar and confident in the treatment and in the SVR12 achieved. Additionally, the length of follow up period would have also had an impact. The costs of untreated HCV in the study by Kieran *et al* were established over a 3-year period and subsequently annualised. In this study, our costs were established over a 12-month period and it would be expected that the resource utilisation would decrease over time and thus, the mean annual costs would reduce.

We completed a literature search to identify other studies that report post-treatment costs. In 2013, Manos *et al* reported post-treatment total (all-cause) costs per person per year of $6,301 (~€5,500) [377]. However, the study did not report HCV-related healthcare costs independently and thus, comparison with our results, which report HCV-related healthcare costs, is difficult. Tandon *et al* reported HCV-related healthcare costs of $3,535 (~€3,110) per patient per year [378]. However, this study included patients who completed therapy with PR alone but did not distinguish between those who achieved a SVR and those who did not.

Despite strong evidence in studies by Innes *et al* and Van der Meer *et al* for improved prognosis with SVR, there has been some contradictory data suggesting that SVR-achievement does not always provide a significant clinical benefit [390-396]. There have been studies that have shown that the risk of disease progression is not eliminated with viral eradication, with some patients experiencing decompensation or the development of HCC despite achieving a SVR [390, 391, 397, 398]. This may explain the higher cost of

diagnostic investigations in patients who achieved a SVR following treatment with the IFN-free regimens. Given the severity of their disease, continued monitoring for disease progression is necessary. Additionally, the WHO recommend screening for HCC with six-monthly ultrasound examinations in persons with cirrhosis, including those who have achieved a SVR [52].

The high cost of inpatient admissions observed in the cohort treated with IFN-free regimens can be justified by the fact that prior to commencing treatment, these patients had advanced liver disease and/or present or previous history of decompensation and that achievement of a SVR12 does not completely eliminate the risk of further disease progression entirely. Of the seven patients admitted during the post-SVR follow-up period, six had a CTP score B/C and three had history of decompensation. These patients had significant liver disease on commencement of treatment and despite achieving a SVR12, continued to experience decompensation and other disease-related complications which contributed to substantial expenditure on HCV-related admissions in this 12-month follow-up period. The sensitivity analysis demonstrated that in the absence of post-treatment admissions, laboratory investigations were the main driver of expenditure in both IFN-based and IFN-free cohorts and more importantly, that the mean annual post-SVR costs in patients with compensated cirrhosis fell to a level that is lower than the costs in untreated HCV.

These data provide evidence of some reduction in HCV-related healthcare costs following a SVR12/24 but expenditure remains significant and raises questions about the financial benefit of treating patients if they continue to accrue substantial costs despite successfully clearing the virus. Given that the WHO recommend bi-annual liver ultrasounds in patients with cirrhosis, it is reasonable to expect some resource utilisation in the post-SVR period but not to the extent that was estimated in this study.

While we did highlight the limitation of comparing expenditure over a 12-month follow-up period with the 3-year period in the untreated cohort, it would be more important to examine the clinical practice of physicians in the treatment units. It would appear that patients without cirrhosis are not being discharged from the clinics despite achieving a SVR and that patients with cirrhosis are undergoing monitoring assessments more frequently than is recommended. The outcomes from this sub-study would suggest that clinical or practice guidelines need to be updated (or developed), physicians should be presented with these data and changes in practice are required so as to stop unnecessary healthcare expenditure which could be used elsewhere.

6.8 Results - Sub-study 3

In total, a sample of 39 patients were included in this study. This included 12 patients who discontinued treatment prematurely while receiving treatment with BOC/PR and 27 patients who were receiving treatment with TPV/PR.

6.8.1 Patient Demographics

The baseline demographic profile of the patients included in this study is presented in Table 37. The cohort was predominantly male (85%) and cirrhosis was present in 23%. The median age was 45 years (IQR 39-54). Patients previously treated with PR accounted for 39%. In those treated with TPV/PR, 30% had previous treatment experience while 22% had cirrhosis. In those treated with BOC/PR, 58% had previously received treated with PR while cirrhosis was present in 25%. There were no statistically significant differences observed in selected characteristics between the TPV/PR and BOC/PR subgroups.

Table 37: Baseline demographic profile of n=39

	Total Cohort n=39	TPV/PR n=27	BOC/PR n=12	*P*-value
Male, n (%)	33 (85)	23 (85)	10 (83)	0.14
Median Age (IQR)	45 (39-54)	43 (39-52)	50 (39-60)	0.886
Treatment Experienced, n (%)	15 (39)	8 (30)	7 (58)	0.094
Cirrhotic, n (%)	9 (23)	6 (22)	3 (25)	0.854
Genotype, n (%)				
GT1	6 (15)	5 (19)	1 (8.5)	0.512
GT1a	30 (77)	20 (74)	10 (83)	
GT1b	3 (8)	2 (7)	1 (8.5)	

6.8.2 Resource Utilisation in the Post-Discontinuation Period

In the 12-month period following premature discontinuation, patients returned for an outpatient clinical assessment approximately 5 times (95% CI 3.4-6.5). During these visits, the patient was seen by a consultant grade physician or doctor-in-training on average 1.7 occasions (95% CI 1.2-2.2) or by a CNS 3.3 times (95% CI 2-4.6). The mean number of blood samples, for laboratory investigations, taken per patient per year was 4.6 (95% CI 3.1-6.2) and patients underwent HCV-PCR assays 1.8 times (95% CI 1.4-2.3) in the 12-month period following discontinuation. Referral to other hospital services was infrequent (Table 38).

Table 38: Resources utilised by patients during the post-discontinuation period

	Total Cohort n=39
OPD Visit	5 (95% CI 3.4-6.5)
Laboratory Investigations	4.6 (95% CI 3.1-6.2)
HCV-PCR Assay	1.8 (95% CI 1.4-2.3)
Referral	0.15 (95% CI 0-0.47)
Admissions (Inpatient days)	0.3 (95% CI 0.06-0.7)
Physician	1.6 (95% CI 1.2-2.2)
Clinical nurse specialist	3.3 (95% CI 2-4.6)

6.8.3 Mean Annual Healthcare Costs in the Post-Discontinuation Period

The mean annual ambulatory care expenditure by a patient who discontinued treatment was €1,119 (95% CI €830-€1,403) (Table 39). Laboratory investigations were the greatest contributor to these costs (41%), with an average expenditure of

€459 per patient (95% CI €325-€605). This was followed by diagnostic procedures and staff, accruing annual mean costs of €217 and €180 per patient, respectively, following premature discontinuation. Liver ultrasounds (38%) and chest x-rays (19%) were the most costly components of the diagnostic procedures.

Table 39: Costs accrued by patients during the post-discontinuation period

	Total Cohort n=39	Presence of cirrhosis n=9	Absence of cirrhosis n=30	*P*-Value
Laboratory Investigations	€459 (95% CI €325-€605)	€864 (95% CI €562-€1183)	€337 (95% CI €207-€472)	0.001
HCV-PCR Assays	€118 (95% CI €92-€146)	€136 (95% CI €83-€186)	€112 (95% CI €81-€151)	0.515
Diagnostic procedures	€217 (95% CI €135-€313)	€403 (95% CI €187-€641)	€161 (95% CI €92-€254)	0.103
Referrals	€19 (95% CI €0-€60)	€74 (95% CI €0-€223)	€3 (95% CI €0-€8)	0.363
Staff	€180 (95% CI €126-€238)	€284 (95% CI €156-€417)	€149 (95% CI €97-€217)	0.057
Admissions	€126 (95% CI €21-€282)	€186 (95% CI €0-€452)	€108 (95% CI €4-€305)	0.654
Total	€1,119 (95% CI €830-€1403)	€1,947 (95% CI €1389-€2456)	€870 (95% CI €615-€1163)	0.001

When stratified according to the presence or absence of cirrhosis, the mean annual laboratory costs and the mean annual total costs in the post-discontinuation period were statistically significantly higher in those with cirrhosis when compared with those without cirrhosis (*p*-value = 0.001 for both laboratory costs and total costs, respectively).

6.8.4 Comparison of the Mean Annual Costs of Untreated HCV and Post-Discontinuation Individuals

We compared the post-discontinuation costs obtained in this study with the mean annual medical costs of untreated HCV reported by Kieran *et al* and the mean annual post-SVR costs reported earlier in this chapter [81]. Kieran *et al* stratified the mean annual costs for untreated HCV into different stages of liver disease. We looked at the costs of untreated HCV and the post-SVR costs after treatment with IFN-based regimens in F0-F3 patients and those with compensated cirrhosis.

There was a statistically significant difference between the mean annual post-discontinuation costs in individuals with F0-F3 fibrosis (mild to moderate disease) (€870) and the mean annual costs of untreated HCV for individuals with mild and moderate disease (€404), as reported by Kieran *et al* (p=0.003) [81]. The difference between the post-discontinuation costs (€1,947) and the costs of untreated HCV (€1,762) were not statistically significant in the cohort of patients with compensated cirrhosis (p=0.850). Additionally, a statistically significant difference (p<0.001) between the mean annual post-discontinuation costs and the mean annual post-SVR costs was observed for both the cohort of patients with F0-F3 disease and those with compensated cirrhosis (Table 40).

Table 40: Comparison between the mean annual costs for the untreated HCV, the post-SVR period and the post-discontinuation period after IFN-based treatment

	Mean annual costs for untreated HCV (Kieran *et al)*	**Mean annual post-SVR costs following IFN-based treatment**	**Mean annual post-discontinuation costs following IFN-based treatment**
F0-F3	€404 (95% CI €354-€458)	€505 (95% CI €378-€661)	€870 (95% CI €621-€1155)
Compensated cirrhosis	€1,762 (95% CI €974-€3229)	€521 (95% CI €308-€764)	€1,947 (95% CI €1359-€2542)

6.9 Discussion: Sub-study-3

In this study, the mean annual post-premature discontinuation ambulatory care expenditure was substantial. In the 12-month window following treatment cessation, patients returned for an outpatient clinical assessment and for laboratory investigations approximately every 2.5 months. These laboratory investigations were the principle driver of the costs (41%) followed by diagnostic procedures. Diagnostic procedures accounted for 19% of the total costs and chest x-rays and liver ultrasounds were the most costly components of these. Despite ceasing treatment, patients continued to return to the outpatient department to undergo laboratory investigations and diagnostic procedures in order to treat the AE that led to the premature discontinuation, to monitor

the HCV infection and liver disease that was not successfully treated and/or to prepare for re-treatment with an alternative regimen.

We compared these data with that reported by Kieran *et al* on the direct costs of untreated HCV infection in Ireland and with the mean annual post-SVR costs reported in this chapter. The mean annual costs following discontinuation in patients with F0-F3 fibrosis was statistically significantly higher than the mean annual cost of untreated HCV. This is likely due to the need to continue to treat and monitor the AEs that resulted in the premature discontinuation. However, in patients with compensated cirrhosis, the mean annual costs of untreated HCV and following post-discontinuation were comparable and no statistically significant difference was reported. We observed that the mean annual costs following premature discontinuation were statistically significantly higher than the mean annual post-SVR costs for both patients with F0-F3 fibrosis and patients with compensated cirrhosis. This highlights the importance of ensuring patient suitability to treatment through appropriate patient selection and pre-treatment education. Premature discontinuation is costly, adding to the already substantial cost of treating patients with DAA-based treatment regimens and mean annual post-discontinuation costs are higher than the mean annual costs in untreated patients. The introduction of the IFN-free regimens has reduced the rate of premature discontinuation substantially, so much so that there was an insufficient sample of patients available from whom we could calculate the cost of discontinuation. Therefore, the budget impact of premature discontinuation is decreasing, ensuring more resources are available for the treatment of patients. These data provide evidence against the use of IFN-based regimens in HCV-infected patients. Both the high rate of discontinuation and the significant HCV-related healthcare costs in the 12-month period following discontinuation, which are greater than the costs of untreated HCV in both the F0-F3

and compensated cirrhotic populations, indicate that withholding treatment until access to the IFN-free regimens is available is a more appropriate use of resources.

6.10 General Discussion

This study reports the substantial real world DAA treatment costs, post-SVR costs and post-discontinuation costs in the Irish setting for both IFN-based and IFN-free regimens. Until now, real world cost data for HCV treatment in Ireland has not been available. Given the rapidly changing HCV treatment landscape, robust real world cost and resource data is essential for evaluating and understanding the costs and benefits of these treatments. Availability of both HCV medication costs and on-treatment costs pertaining to patient monitoring, management of AEs and inpatient admission, post-SVR and post-discontinuation cost will benefit those preparing submissions to HTA agencies, who have previously relied on out-dated data from other jurisdictions [399].

Some observations were remarkable, in particular, the significant expenditure on patients despite achieving virological clearance. The costs estimated would question the benefit of treating these patients if, as determined, the costs after SVR are comparable or higher than those costs in patients who did not receive treatment. These outcomes would suggest that there is a need to change, or implement, clinical guidelines for managing patients after viral eradication. These guidelines need to define the frequency of post-SVR assessments, the assessment process itself and the stage at which a patient should be discharged from care. In instances where the patient will require continued monitoring, for example in patients with cirrhosis, a clearly defined assessment pathway is required to ensure appropriate use of resources.

The use of IFN-based regimens continues to be recommended in some patient cohorts, particularly those with F1-F2 fibrosis. However, the substantial costs of the management of DAA- and PR-related adverse events, the high discontinuation rate and the costs reported for the post-premature discontinuation period merit reviewing whether, from a cost perspective, patients should be treated with IFN-based regimens, irrespective of the disease severity. Incorporating these data into a cost-analysis may indicate that the cost of treatment with the IFN-based regimens is, in fact, comparable to treatment with IFN-free regimens.

This study has several strengths and limitations. To our knowledge, the results reported for the IFN-free cohort are the first to estimate the direct treatment costs and post-SVR costs for a cohort with advanced liver disease treated with IFN-free regimens. It is also the first to present detailed estimates of the on-treatment monitoring and management costs for both IFN-based and IFN-free regimens. These data have proved valuable, as demonstrated by their inclusion in recent HTA submissions to the NCPE [400]. Additionally, the availability of patient level data from the study by Kieran *et al* facilitated the analysis for statistical significance between the untreated and post-treatment costs. Societal costs are not considered in the study as we focused on the direct medical costs from the payer's perspective.

In these costing studies, we included all patients for whom we could collect comprehensive resource utilisation data. Data collection for these studies involved additional site visits and extensive searching of patient charts and the hospital electronic records. In some treatment units, access to electronic patient records was limited and therefore, we were unable to capture sufficient utilisation data for inclusion into the study. Additionally, in all sub-studies, particularly in the post-discontinuation study, there were patients who were lost to follow-up, mainly as a result of disengaging

from the clinical services, and were therefore not captured in the analysis. This is despite us undertaking further analysis within the hospital electronic records and identifying that these patients had not engaged with other services within the hospital over the course of our study period. While the registry enabled us to investigate whether these patients attended hepatology or infectious disease units in other hospitals, the lack of data linkage prevented us from identifying whether they engaged with other services in alternative hospitals. The analysis of costs in this study focused on HCV-related healthcare expenditure, which included the costs of referral and investigations carried out by other services/hospital departments for the treatment of co-morbidities or side effects relating to their HCV. However, the cost of treating other, non-HCV related conditions (e.g. cancer, diabetes etc.) was beyond the scope of this study.

Additionally, while there may be perceived limitations when it comes to the generalisability of cost studies outside of the healthcare system in which they were conducted, the information provided in this study will allow others to adapt the methodology and apply unit costs reflective of their healthcare system, reinforcing the applicability of this data outside of Ireland.

6.11 Conclusion

This study reports the cost of IFN-based and IFN-free therapy in real world practice in Ireland. It provides valuable information about the mean cost per treatment, the cost per SVR, the cost-consequences of premature discontinuation and the HCV-related healthcare costs following successful treatment with DAA treatment regimens. These up-to-date data form a comprehensive assessment of the real world costs of treating HCV infection in Ireland. This provides information beneficial to decision-makers involved in reimbursement and health policy in the post-reimbursement era and for use

in future economic evaluations of HCV regimens (e.g. elbasvir and grazoprevir) in Ireland.

Additionally, we provide evidence to support the implementation of guidelines for the treatment and discharge of patients. There is significant variation in the resource utilisation by patients while on treatment and utilisation remains substantial in the 'follow-up' period after treatment. While ensuring that they provide the best, and most appropriate, level of care, physicians need to consider the consequences of inappropriate resource utilisation. Guidelines should outline the frequency of patient assessments, the investigations and tests to be undertaken at each assessment and a timeline for discharging patients after successful treatment. Overuse of resources will impact the healthcare budget and the number of patients that can be treated. It is in the interested of the treating physicians, and the HSE, that guidelines are developed and adhered to, to ensure optimal allocation of the HCV drugs budget.

Chapter 7

Chapter 7 Attitudes and Perceptions of Stakeholders to the Irish Hepatitis C Treatment Registry

7.1 Introduction

The Irish national HCV treatment registry, established in 2012, was the first national registry in Ireland with multidisciplinary involvement. The aim of this registry was to determine the real world effectiveness and economic impact of drug treatments licensed for use in HCV infected patients in Ireland. There are many stakeholders who have had input into the development of the registry and the analysis of the outcomes to date.

Given the long-term commitment of resources associated with the development and operation of a registry, it is important to evaluate the registry itself, to ensure that it is meeting its objectives in an efficient manner, but also to evaluate the perception and attitudes of stakeholders to the registry. Optimal use of the registry is important to ensure that the research output is used and disseminated appropriately to drive policy within the health service and to enhance the quality of care among providers. In order to be of optimal use within the health services, there must be an awareness of, and access to, these data [401].

A number of studies have assessed provider perception to registries and found both positive and negative attitudes towards them. A lack of training, cost and time were identified as barriers to their use [402-404]. The continued success of the national HCV registry depends on the support of the stakeholders, identification of the perceived value of the registry, the recognition of areas for improvement and implementation of these findings to facilitate better registry operation and use. Given that it has now been four years since the HCV registry was established in Ireland, the overall aim of this study was to determine the perception, knowledge and attitudes to the HCV treatment

registry in Ireland among key stakeholders. The objectives of this study included assessment of:

- The perceptions around the purpose, benefits and value of the registry
- The experience with the operational aspects of the registry
- The key areas for improvement
- The knowledge around key terms relating to generation of evidence for therapeutic interventions

7.2 Methods

Quantitative survey methodology was used to achieve the study end-points. Two surveys were developed: one for non-nursing clinical and non-clinical stakeholders (henceforth described as the non-nursing stakeholders) and one for nursing stakeholders. Stratifying the stakeholders was justified based on the clear differences between the two cohorts in terms of involvement in the registry. Choice of questions was derived from other similar studies and modified following piloting [402, 403, 405, 406]. Surveys consisted of a mixture of open and closed-questions. Multiple-choice questions were designed to allow more than one option to be selected. Surveys were piloted on a sample of stakeholders from both cohorts prior to dissemination. Feedback from the pilot phase was considered and incorporated into the surveys, where appropriate. Surveys contained 25 (non-nursing stakeholder survey) and 26 (nursing survey) items in total. The surveys consisted of questions on respondents' demographics, their familiarity with the registry and their perceptions and attitudes towards the registry. Ethical approval for the study was obtained through the St. James' Hospital/Tallaght Hospital Research Ethics Committee (No. 2016/05/09).

Purposive sampling methods were used to identify stakeholders to facilitate data collection. The sampling frame for the non-nursing stakeholder survey was drawn from

current members of ICORN, while the sampling frame for the nursing survey was the Irish Hepatology Nursing Association (IHNA) with the addition of CNSs in infectious diseases. All respondents completed an online survey administered through Survey Monkey™.

Identified stakeholders were invited to participate through a personal email with a link to the online web URL. A second reminder email was sent to all selected for participation two weeks after the initial invitation email was distributed.

7.2.1 Data Collection and Analysis

Survey data was downloaded from the online website (Survey Monkey™). Narrative data received in response to open-ended questions underwent a process of enrichment where applicable, and answers were categorised based on identified themes. The narrative responses were read and re-read to capture an overall sense of the information provided. Themes and sub-themes were then established. Final datasets were imported into SPSS Version 21 (IBM Corp, Armonk, NY, USA) for descriptive analysis.

7.3 Results

7.3.1 Response Rate

A total of 28 individuals responded to the survey and were included in the analysis (response rate 39%); 16 responded to the non-nursing survey (response rate 33%) while 13 responded to the nursing survey (50% response rate).

7.3.2 Demographic Profile of Respondents

In the non-nursing survey, 46% (n=7) of the respondents were physicians (consultant-grade or doctor in-training), 27% (n=4) were pharmacists and 27% (n=4) were researchers or scientists. The roles of the nursing respondents spanned CNSs, staff nurses and specialist research nurses. HCV and infectious diseases were the most commonly reported areas of practice (54% (n=15) and 25% (n=7), respectively). Other areas of practice included virology, immunology and transplantation while three respondents reported 'other' as their area of practice. The mean number of years that respondents had been working in their area of practice was 12 years (range 2-28 years), with the majority having between 11-15 years of experience in this area of work (29%, n=8).

7.3.3 Role in the HCV Treatment Registry

The majority of respondents reported having more than one role in the HCV registry (75%, n=21), spanning both clinical and operational aspects.

7.3.3.1 Non-nursing Stakeholders

Clinical roles described by the non-nursing respondents included treatment of patients with DAA-based regimens (60% (n=9)), education of patients prior to and during treatment with DAA-based regimens (33% (n=5)), and supply of medications and pharmaceutical care to patients treated for HCV infection with DAA-based therapies (13% (n=2)). Three respondents were involved in virological testing (13%, n=2) and immunological testing (7%, n=1) of patients prior to and during treatment.

Involvement in the operational aspects of the registry encompassed interpretation and review of treatment outcomes (27% (n=4) and 13% (n=2), respectively) and data input

and maintenance of the registry (7%, n=1). In addition, over half (53% (n=8)) of the respondents were involved in research projects for patients with HCV infection facilitated by the registry (Table 41).

7.3.3.2 Nursing Stakeholders

Some 90% of the nursing staff reported involvement in both the education and treatment of patients with DAA-based regimens (92% (n=12) and 92% (n=12), respectively). Additionally, 54% (n=7) of nurses took blood samples for patients receiving treatment.

This cohort played a significant role in the operational aspects of the registry. The majority were involved in the patient registration process (85%, n=11) and 77% (n=10) reported involvement in the patient consent process. Other operational roles included the collation of and review of outcomes of patients during and following completion of treatment (46% (n=6) and 39% (n=5), respectively) (Table 41).

Table 41: Roles of stakeholders in the HCV treatment registry

	Non-nursing stakeholders n/N (%)	**Nursing stakeholders n/N (%)**
Treat patients	9/15 (60%)	12/13 (92%)
Educate patients	5/15 (33%)	12/13 (92%)
Provide pharmaceutical care	2/15 (13%)	N/A
Virological testing	2/15 (13%)	N/A
Immunological testing	1/15 (7%)	N/A
Blood samples	N/A	7/13 (54%)
Register patients	N/A	11/13 (85%)
Obtain consent	N/A	10/13 (77%)
Collate outcomes	N/A	6/13 (46%)
Review outcomes	2/15 (13%)	5/13 (39%)
Interpret outcomes	4/15 (27%)	N/A
Other research projects	8/15 (53%)	N/A
Other	1/15 (7%)	0/13 (-)

N/A – Not applicable – This question was not asked in the survey
Respondents were able to select more than one option in answering this question

7.3.4 Non-nursing Survey Results

7.3.4.1 Perceived Purpose

The majority of respondents considered monitoring of treatment outcomes as one of the main purposes of the registry (93%, n=14). The ability to assess the cost-effectiveness of treatments (80%, n=12) and to allow robust research studies to be undertaken (80%, n=12) were two other frequently selected purposes (Table 42).

Table 42: Perceived purpose of the registry

	Non-nursing stakeholders n/N (%)	Nursing stakeholders n/N (%)
Monitor patient numbers	10/15 (67%)	13/13 (100%)
Monitor outcomes	14/15 (93%)	13/13 (100%)
Monitor AEs	3/15 (20%)	8/13 (62%)
Identify gaps in service provision	5/15 (33%)	7/13 (54%)
Provide up-to-date data for policy-makers	8/15 (53%)	11/13 (85%)
Evaluate the evolution of the registry	10/15 (67%)	11/13 (85%)
Assess the cost-effectiveness of treatments	12/15 (80%)	1/13 (8%)
Allow for robust research studies	12/15 (80%)	N/A

N/A = Not applicable – This selection was not available in the survey
Respondents were able to select more than one option when answering this question

7.3.4.2 Perceived Benefits

All respondents reported the ability to assess real world effectiveness of the DAA treatment regimens as a benefit of the registry. The ability to compare the Irish outcomes with those of other countries (73%, n=11) and the ability to longitudinally follow-up patients treated for HCV infection (73%, n=11) were cited as additional benefits. Table 43 presents all the benefits that were reported, stratified by stakeholder respondents.

Table 43: Perceived benefits of the HCV treatment registry

	Non-nursing stakeholders n/N (%)	Nursing stakeholders n/N (%)
To assess the real world effectiveness of DAA-based HCV treatment regimens	15/15 (100%)	12/13 (92%)
To assess the real world costs of DAA-based HCV treatment regimens	10/15 (67%)	11/13 (85%)
To assess the rate of AEs	5/15 (33%)	6/13 (46%)
To provide visibility and transparency of treatment outcomes	0/15 (0%)	10/13 (77%)
To compare Irish real world outcomes with those of other countries	11/15 (73%)	11/13 (85%)
For effective management of resources	6/15 (40%)	9/13 (69%)
For efficient allocation of resources	5/15 (33%)	9/13 (69%)
A rich source of research on patients treated with DAA-based HCV treatment regimens	10/15 (67%)	0/13 (0%)
The ability to longitudinally follow-up patients treated with HCV	11/15 (73%)	0/13 (0%)
To biobank samples	5/15 (33%)	0/13 (0%)

Respondents were able to select more than one option in answering the question

7.3.4.3 Perceived Value

Overall, 93% (n=14) of respondents believed that the registry was a 'highly valuable' tool. The remaining respondent reported that it was 'somewhat valuable'. The consensus amongst this cohort was that the outcomes from the registry were important to the respondents in their work with 73% (n=11) who felt that the outcomes were 'very' or 'extremely' important.

Narrative comments which were suggestive of potential ways of enhancing the value of the registry included the development of an electronic platform which would allow patient registration, approval, consent and treatment data (treatment regimen of choice, treatment start date, date of treatment completion and outcomes) to be inputted instantaneously at each site, thus, streamlining the administration processes and facilitating data accessibility.

"…easier input and access to data (via an App perhaps)"

"Ideally, an electronic platform accessible to nurses, physicians etc. at all treatment sites….allowing outcomes to be inputted instantaneously…..reduce paperwork"

"By utilising a digital, user-friendly system to obtain data from sites"

The respondents described the need for clearly defined research goals, an improved process for accessing data for further research studies and publication or presentation of the research findings in international peer-reviewed journals or at international conferences as additional ways to enhance the value of the registry.

"…a formal process for submitting research proposals that would utilise the registry data"

Other ways in which the non-nursing stakeholders felt that the registry could be enhanced were through improvement of the communication of outcomes and facilitating data sharing between each treatment site.

"More accessibility to the data at a local level"

"Improved accessibility of outcome data"

Additionally, inclusion of all HCV patients and greater participation and involvement were cited as ways to enhance the registry. One clinician believed the value of the registry would be enhanced if it received adequate recognition from policy-makers.

"….official recognition by the HCV treatment programme"

"….expand it to all HCV patients"

and

"Greater buy-in at each treatment site"

7.3.4.4 Concerns

When asked to select the issues that concerned them the most about the registry, 60% (n=9) highlighted time as an issue and 27% (n=4) felt that communication of outcomes amongst the stakeholders was a concern that required action.

Registry activities, including the patient registration and patient consent process, resulted in an increased workload for 40% (n=6) of the non-nursing stakeholders. Despite this, respondents often felt that the drawbacks were outweighed by the benefits.

"I am interested in being an active member of the network. It does not increase my workload significantly, or to the extent that it would discourage my involvement"

"The paperwork adds to my workload. However, this brings benefits which outweigh the time cost"

The remaining 60% (n=9) did not indicate that the registry increased their workload. Of those who reported that the patient registration and consent process was applicable to them (n=3), 67% (n=2) reported a 'mostly or altogether' positive experience while 33% (n=1) reported a 'neutral' opinion.

In addition to the issues outlined above, narrative comments brought additional concerns to light. These included

"Appropriate biobanking of samples"

"Timely receipt of information on patients started treatment and subsequently, their outcomes"

There was also concern expressed about the ability to utilise data samples for further research, low levels of stakeholder participation and the reporting of outcomes to a wider, international audience.

"Ability to utilise data samples in research"

"Stakeholder buy-in and involvement"

"….disseminate the research output to a wider, international audience in a timely manner"

7.3.4.5 Areas Identified for Improvement and/or Change

The HCV treatment registry currently operates an 'opt-in' consent process. An opt-out process was considered to be beneficial by 87% (n=13) of respondents. There were a number who were unsure or not in favour of an 'opt-out' consent process. One physician felt that an opt-out process would reduce the quality of data collected.

"It will result in poorer data capture and detract from the validity of the end research. If you are going to do it, you need to do it properly"

The patient registration process was identified as a key area for improvement (53%, n=8). All those involved in patient registration were in favour of utilising an electronic registration process. Other areas identified were the communication pathways amongst all stakeholders (60%, n=9) and the accessibility to the data (40%, n=6) (Table 44).

Table 44: Key areas for improvement in the HCV treatment registry

	Non-nursing stakeholders n/N (%)	Nursing stakeholders n/N (%)
Operational		
Reduction in paperwork/administration	0/15 (0%)	10/13 (77%)
Patient consent process	2/15 (13%)	5/13 (39%)
Patient registration process	8/15 (53%)	0/13 (0%)
Training	1/15 (7%)	4/13 (31%)
Implement an electronic registration and approval process	1/15 (7%)	0/13 (0%)
Additional staff to collect data	0/15 (0%)	1/13 (8%)
Other		
Feedback of treatment outcomes	5/15 (33%)	8/13 (62%)
Communication	9/15 (60%)	0/13 (0%)
Accessibility of data	6/15 (40%)	1/13 (8%)
Participation of stakeholders	1/15 (7%)	0/13 (0%)

Respondents were able to select more than one option in answering the question

Stakeholders were asked about the perceived importance of individual health identifiers (IHIs). All respondents reported that they felt the introduction of these identifiers were important (27%, n=4) or very important (73%, n=11) for the registry and future health services research.

7.3.4.6 Knowledge of Key Terminology[§]

The respondents to the non-nursing survey (n=15) had a very clear understanding of the differences between these RCTs and observational studies with 93% (n=14) providing a correct assessment of the differences between them. The majority identified the low risk of bias associated with RCTs while recognising that observational studies utilised a real world population with less stringent inclusion and exclusion criteria. Similarly, 87% (n=13) were able to clearly distinguish between efficacy and effectiveness.

7.3.5 Nursing Survey Results

7.3.5.1 Perceived Purpose

All nursing staff reported the monitoring of the number of patients receiving treatment and the monitoring of treatment outcomes as a purpose of the registry. Additionally, many reported that one of the purposes was to provide up-to-date data for use by policy-makers with responsibility for planning and evaluating health services (85%, n=11) and to evaluate the evolution and implementation of the HCV treatment program (85%, n=11). Other perceived purposes are presented in Table 42.

7.3.5.2 Perceived Benefits

The ability to assess the real world effectiveness of the DAA-based treatment regimens was the most commonly perceived benefit of the registry (92%, n=12) in this group. Other frequently reported benefits were the ability to assess the real world costs of treatments (85%, n=11) and the ability to compare Irish real world treatment outcomes

[§] The RCT is a trial in which subjects are randomly assigned to one of two groups: one (the experimental group) receiving the intervention that is being tested, and the other (the comparison or control group), receiving an alternative (conventional/placebo) treatment. Appropriately designed RCTs report treatment "efficacy", a measure of the capacity of a treatment to produce the desired effect in a controlled environment Observational research involves the direct observation of individuals in their natural setting and report treatment "effectiveness" Effectiveness refers to "the extent to which a drug achieves its intended effect in the usual clinical setting".

with those of other countries (85%, n=11). Table 43 presents some other benefits that were reported by respondents.

7.3.5.3 Perceived Value

Nursing respondents felt that the registry was a valuable tool with 77% (n=10) stating that it was 'highly valuable' and 23% (n=3) felt it was 'somewhat valuable'. Within this cohort, 54% (n=7) believed that the outcomes were important to their work. The remaining six respondents felt they were 'moderately' (39%, n=5) or 'slightly' (8%, n=1) important.

Narrative comments suggested a number of ways that the value of the registry could be enhanced. These included the establishment of an electronic platform for patient registration or provision of additional staff whose role was to collect data from each treatment site, exclusively, therefore reducing the workload of the nursing staff.

"An online system….it would streamline the referral process"

"….if there was one person collecting data for all treatment centres…..like that of the state-infected patients".

Improving access to data and communication pathways were also commonly cited as ways to enhance the registry.

"…..hear outcomes from other centres"

"easier access to the information….improve information sharing"

"if the database was set up in such a way that the information could be accessed by us all"

7.3.5.4 Concerns

Time (92%, n=12) and the additional paperwork (92%, n=12) were the most commonly reported concerns amongst the cohort of nurses. Gathering of treatment outcomes (54%, n=7), which was often duplicating workload, communication of data amongst stakeholders (39%, n=5), being provided with sufficient information about ones role (15%, n=2) and data protection (15%, n=2) were also reported.

All nursing staff respondents stated that since the introduction of the registry, their workload had increased due to the additional paperwork that was required to be submitted. They felt overwhelmed by the volume of paperwork that was required for registering a patient for treatment and an electronic process was suggested as a way to streamline this aspect of their role.

"Paperwork, would be nice to be electronic"

"The forms require a lot of information. There are several forms to be filled out and faxed"

The entire cohort had experience with the patient registration process and 77% (n=10) found it to be a 'mostly or altogether' positive experience while the remaining 23% (n=3) reported a 'neutral' opinion. Eleven respondents reported experiencing the patient consent process, with 82% (n=9) stating that it was a positive experience and 21% (n=3) reporting a 'neutral' opinion.

7.3.5.5 Areas Identified for Improvement and/or Change

All respondents were in favour of an online electronic patient registration process. When asked, 77% (n=10) felt that a transition to an 'opt-out' process would be beneficial while 23% (n=3) were unsure, and stated that they would like further

information before making a decision, or were not in favour of an 'opt-out' consent process. These respondents felt it was important that patients were informed about the registry and understood the process.

"I think it is important for patients to understand the ICORN process. It is a time to explain all this to them and also for them to understand their data is collecting anonymously"

"Is there a legal precedent for this? I see patient consent as an important issue"

A reduction in the volume of paperwork/administration (77%, n=10) was the most frequently cited operational aspect of the registry that required improvement in addition to the patient consent process (39%, n=5). The timely feedback of treatment outcomes (62%, n=8) was also highlighted as an area for improvement by this group (Table 44).

The nursing staff were asked whether assistance on data management skills and setting up in-house databases would be useful to them. Ten respondents (77%) felt that this would be helpful while three (23%) were undecided as to whether this would be beneficial. Training on data management skills (40%, n=4), upgrading of current in-house databases (30%, n=3), setting up an in-house database (20%, n=2) and the provision on a data collector (10%, n=1) were the types of assistance that would be of value to them.

All respondents considered the introduction of IHIs to be an important (54%, n=7) or very important (46%, n=6) step for the continued success of the registry.

7.3.5.6 Knowledge of Key Terminology

Over two-thirds of nursing staff respondents (69% (n=9)) recognised many of the basic characteristics of RCTs such as the random allocation of treatment arms and the reduction in bias, while 15% (n=2) understood the concepts of an observational study. A number reported that observational studies did not include any interventions or treatments. Two respondents correctly identified the differences between efficacy and effectiveness.

7.3.6 Overall Satisfaction with the HCV Registry

Overall, between the two cohorts, 79% (n=22) were satisfied with their involvement in the registry while 21% (n=6) were undecided. The level of satisfaction with the registry was similar between the two groups (Figure 39).

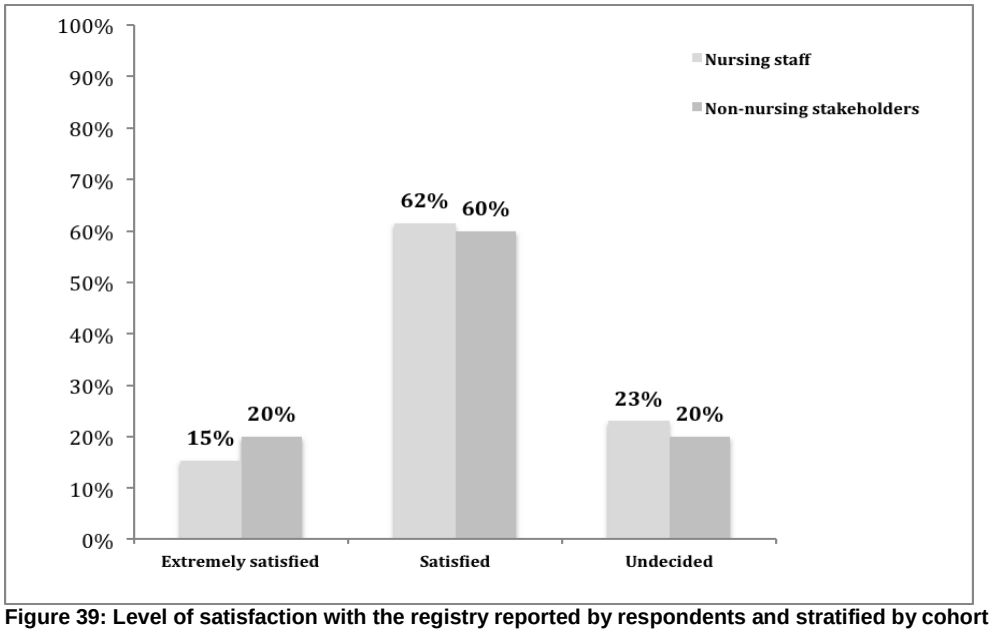


Figure 39: Level of satisfaction with the registry reported by respondents and stratified by cohort

A number of satisfied respondents provided more detailed answers.

"Membership of the network has been very beneficial on a personal and professional level, both for me as an individual and for my institution"

"The registry is an excellent example of how well designed data collection can inform national treatment guidelines…..which ultimately improve patient outcomes…"

"It is fundamental to the whole treatment process currently and for identifying future needs of HCV management in Ireland"

Others, undecided about their level of satisfaction, reported the challenges they found with their involvement such as the extensive barriers that appear to be in place to access data and report research outcomes and the need for additional resources (financial and staff) to continue to expand the role of the registry.

"….too many barriers to overcome in order to access data and report research outcomes internationally.."

"At present, I feel I cannot give it the time it requires"

"Information is not being disseminated. Large amounts of data, which have been collected locally at the request of ICORN, have not been collected"

"The registry is a fantastic tool that can be utilised better and more efficiently…room to improve which may require additional resources such as staff and funding…"

7.4 Discussion

The aim of this study was to determine the perception, knowledge and attitudes to the HCV treatment registry in Ireland among key stakeholders. Our findings suggest that the majority of respondents believed the registry to be a highly valuable tool and that the outcomes are important to their practice. The overall attitude of stakeholders was one of positivity while also providing clear feedback on areas for improving and enhancing the value of this tool.

There were wide variations in views about the purpose and benefits of the registry. However, most respondents recognised the monitoring of the number of patient receiving treatment and the monitoring of treatment outcomes as the primary roles. When we compared the two surveys, responses were significantly polarised, reflecting the different roles that nursing staff play in comparison to the non-nursing stakeholders in the operation of the registry. A larger proportion of nursing staff reported playing a role in the operational aspects, such as patient registration, patient consent and collating outcomes when compared with the non-nursing stakeholders. Given that the survey of non-nursing stakeholders did not include those with patient-facing roles exclusively, i.e. many were researchers or scientists, it was expected that the roles of this cohort would be more varied, with a large proportion reporting roles in HCV-related research.

An area of particular concern highlighted by this study was the perceived increase in workload, mainly due to additional administrative tasks, that was reported by nursing staff. The patient registration process was a particular issue of concern. It was felt that, in order to become more efficient and less time-consuming, an online registration system was required to be developed. Many respondents, from both survey cohorts, suggested that an electronic platform (potentially via an App), that is easy-to-use and accessible at all treatment sites and by ICORN operations, be developed. This would facilitate the processing of patient registration and reimbursement approval and allow treatment details such as the start date, the end date, the outcome and any other relevant details to be uploaded in a simple and time-efficient manner. It would prevent the potential for duplication of patient registration and workload. Other issues reported, which are essential to the continued evolution and success of the registry were communication and accessibility to the data. A number of respondents felt that the channels of communication were currently inadequate. They believed that the reporting

and dissemination of outcomes was not being communicated to all treatment centres and this was impacting stakeholder buy-in and participation. In addition to this, there was a view that there should be better and easier access to the data that could be utilised by stakeholders for their own research.

The study findings established ways in which the value of the registry can be enhanced. Three key themes, which have already been discussed, were identified. Firstly, the development of an electronic platform, accessible at each treatment site was a common finding throughout this survey. While this may be a resource-intensive solution, it is clear that the current system is too demanding on the nursing staff who do not have sufficient time to complete the operational registry roles required of them, as they currently stand. Therefore, an electronic platform that improves efficiency and lowers the workload of stakeholders is key to optimising the number of patients registered, approved and receiving treatment and the 'real-time' reporting of outcomes. The second theme identified for enhancing the value of the registry is the formation of a formal process for submitting research proposals and gaining access to the data. Providing greater access to the data has the potential to increase collaboration amongst stakeholders and improve the overall quality of the research. Finally, issues relating to communication frequently arose. Respondents want clearer communication pathways with regular updates on the research studies in progress and the outcomes from these studies. There was particular emphasis on the requirement for the reporting of site-specific outcomes and comparison between treatment sites.

Respondents understanding of the differences between RCTs and observational studies and efficacy and effectiveness between the two survey cohorts was analysed. The level of understanding between the two cohorts was diverse. This suggests the need to provide better education or information to stakeholders about these study

types, about the registry and the impact of the findings on health-policy. This will increase the overall knowledge-base of stakeholders. A better understanding of these research methods may potentially lead to greater stakeholder involvement and participation with the registry.

Overall, findings suggest that the majority of stakeholders (79%) were satisfied with their involvement in the registry and recognise the benefit and value of their participation. However, the challenges and areas for improvement identified were the key findings from this survey. Acting on these findings and making the necessary changes are required in order to ensure the continued success of the registry.

By seeking the opinions from key stakeholders and by working to improve the issues that have been raised in this survey, we are be confident that this will lead to improved stakeholder participation, enhance the value of the registry and lead to more robust research outcomes.

7.4.1 Limitations

While this study investigated the attitudes and perceptions of key stakeholders to the national HCV registry in Ireland, it had some limitations. Although a response rate of 39% is considered high, those who took the time to complete the survey may not be representative of the entire group of registry stakeholders. In particular, the view of physicians may be under-represented in this study.

An additional limitation of the study was the familiarity of responders to the registry. All respondents considered themselves familiar with the registry. However, it is possible that many of those not familiar with the registry did not respond.

Finally, the option for respondents to select more than one answer to a number of questions may reduce the impact of these questions. A limit of three answers on the questions relating to the role of the respondent, the purpose, the benefits and the concerns regarding the registry may have resulted in a clearer view of both respondents understanding of the registry and priority action points for improvement. This was not identified as an issue during the pilot-testing phase.

Despite this, a useful insight into the views of stakeholders has been obtained and key areas for enhancing the value have been identified.

7.5 Conclusions

The findings of this study identified the high level of satisfaction with the registry and the high level of value that stakeholders place on the Irish national HCV treatment registry. The existing concerns of stakeholders provide a helpful insight into the difficulties that they currently face, the barriers to their involvement and identified key areas for improvement that will ultimately enhance the value of the registry. There is a clear need to improve the efficiency of the operational aspects of the registry for nursing staff and to improve the communication amongst all stakeholder. Communication is fundamental to the success of the registry and a commitment to promote better channels of communication for the reporting and dissemination of the research outcomes is necessary.

The existing positivity towards the registry, combined with taking the necessary action on the priority points identified, should result in the continued success of the national registry, a tool that is fundamental to the treatment and management HCV infection and the reimbursement of HCV drugs in Ireland.

Chapter 8

Chapter 8 Practical Applications Using Observational Data from the National HCV Treatment Registry

8.1 Introduction

Analytical methods used in the healthcare decision-making process often rely solely on data from RCTs. NMAs, which have the ability to estimate the relative treatment effect of multiple treatments simultaneously in the absence of head-to-head studies, traditionally include data from RCTs, exclusively [252, 263]. However, these data can have limited generalisability to the clinical setting and the inclusion of observational data in the NMA may improve the applicability of the relative treatment effect to the real world setting.

Economic modelling is an approach that is frequently used to estimate the cost-effectiveness of new and existing healthcare interventions. It provides a long-term outlook of healthcare costs and gains, extrapolating from available short-term data [147]. Given that these models are required by HTA agencies to facilitate reimbursement decisions before sufficient and country-specific observational data is available, they are typically populated with data from RCTs and published literature and make the assumption that the clinical effectiveness will mirror the clinical trial efficacy. The limitations of such an approach are acknowledged and the impact that this may have on the estimation of the cost-effectiveness of these therapies and subsequent reimbursement decisions is recognised.

Prior to undertaking the research for this thesis, there was no data available on the clinical effectiveness or the real world HCV-related treatment costs for DAA regimens in the Irish setting. In this chapter we aim to:

- Part 1: Assess the impact of including observational data in the network meta-analysis[**]. The NMA was informed by the systematic literature review study reported in *Chapter 4* with the addition of outcome data generated in *Chapter 5.*
- Part 2: Assess the impact of including the estimates of clinical effectiveness (*Chapter 5)* and HCV-related treatment costs (*Chapter 6),* derived from this thesis, on the cost-effectiveness of TPV/PR and BOC/PR. These estimates were inputted into an independently produced economic model designed by a colleague in the NCPE. The aim of this model was to directly compare the cost-utility of these two agents in the Irish setting.

8.2 Part 1: Network Meta-Analysis

8.2.1 Methods

The systematic literature review presented in *Chapter 4* was reported in accordance with the PRISMA criteria [292]. Three thousand, three hundred and seven records were identified from PubMed, EMBASE and conference proceedings. Following the application of eligibility criteria, 86 studies, which reported the efficacy or effectiveness of ten different treatment regimens, were selected for inclusion [97-105, 110-113, 116-118, 121, 123-130, 157, 289, 290, 298-355]. The ten treatment regimens identified were TPV/PR, BOC/PR, SMV/PR, SOF/PR, DCV/PR, SOF+RBV, SOF/SMV±RBV, 3D±RBV, SOF/LDV±RBV, and SOF/DCV±RBV.

Despite efforts to contact the authors, there was insufficient data on the proportion of patients with cirrhosis in fourteen observational studies, a characteristic required by

[**] Joy Leahy, a PhD student in statistics in Trinity College, Dublin, assisted with the technical work for the development of this model. A network meta-analysis, using Bayesian methodology was considered the most appropriate method for pooling this data. The computation and statistical skill required for this analysis was considered to be outside the expertise required by the candidate for this thesis. The work for this study required novel matching methods and models to be developed in order to form a connected network. For this piece of work, the candidate was responsible for the generation, collation and preparation of inputs for use in the model. The candidate completed all background work, systematic reviews, data extraction, author contact and applied clinical knowledge to made decisions around the inclusion/exclusion criteria and adjustments that were required to the model to account for the presence of cirrhosis and the tendency for observational data to be more bias than clinical studies.

Leahy *et al* to connect the networks [407]. Therefore, 72 studies from the systematic review were suitable for inclusion in this NMA.

In order to form a connected network, single-agent, non-comparative studies, both clinical trials and observational studies, were matched as proposed by Leahy *et al* [407]. In the absence of matching, a disconnected network would have formed, preventing the estimation of the relative treatment effect for all ten treatment regimens.

Bayesian NMA models were fitted using MCMC simulation in OpenBugs3.2.3. As we aimed to estimate the clinical effectiveness of licensed regimens for the treatment of GT1 HCV infection and examine the impact of including observational studies in evidence synthesis, a number of NMA models were run, with and without the inclusion of the observational studies.

The MCMC simulation in OpenBugs facilitates the determination of the ranking of each treatment. It calculated the probability of each treatment being in the n^{th} position or better. The probabilities were plotted on a rankogram and the surface under the cumulative ranking curve (SUCRA) was calculated. The SUCRA provides a summary statistic for the cumulative ranking. It reports a percentage rank for each treatment, which is calculated based on the area under the curve for each regimen as a proportion of the total area under all the curves in the cumulative rankogram.

The log odds ratio (LOR) for each treatment regimen versus PR was presented. This is a measure of the association between an exposure (treatment) and an outcome (SVR). The credible interval (CrI) is the Bayesian statistical measure of uncertainty similar to

confidence intervals. If the credible interval does not span 0 then we can conclude that the treatment is statistically significantly better than PR.

8.2.1.1 Role of the Candidate

While an understanding of the methodology applied in this study is known by the candidate, the computational skills required was considered to be outside the expertise required for this thesis. The clinical knowledge of the candidate was necessary in order to complete the analysis. The role played by the candidate in this study is outlined below.

- Background work
    - Identification of all treatment regimens licensed for use in GT1 HCV infection.
    - Literature search to identify any previously published HCV-related NMAs.
- Systematic literature review
    - Design the protocol and undertake the systematic literature review reported in Chapter 4. These data were required to inform the NMA.
- Data extraction
    - Extract all relevant data from the literature identified in the systematic literature review. This included, where possible, the separation of data for patients with and without cirrhosis when it was reported in a mixed cohort.
- Author contact
    - Contacting authors of published literature when necessary, or relevant, data was not published in the literature.

- Exclusion/Inclusion criteria
    - Selecting the criteria and subsequent studies for inclusion in the NMA.
- Application of clinical knowledge
    - Advising about the incorporation of terms in the model that would account for the presence or absence of cirrhosis in patients.
    - Advising about the appropriate pooling of data from included studies. For example, the statistician designing the model found that pooling of studies that included patients treated with SOF+RBV with studies that included patients treated with SOF/PR together was the best method for forming a connected network. However, the candidate identified that these were, in fact, two different treatment regimens and could not be pooled together, from a clinical perspective.
    - Advising that data from observational studies is subject to greater bias than RCTs and therefore, this data should be down-weighted to reflect this bias.

8.2.2 Results

8.2.2.1 Clinical Trials – Excluding Observational Data

Overall, 20 RCTs with a comparator group and 23 single-agent, non-comparative clinical trials, identified in the systematic literature review in *Chapter 4,* were included in this analysis.

The first model included data from the 20 RCT studies (Figure 40). The ELECTRON study was not connected to the remainder of the network and therefore SOF/LDV±RBV and SOF+RBV were excluded from this analysis.

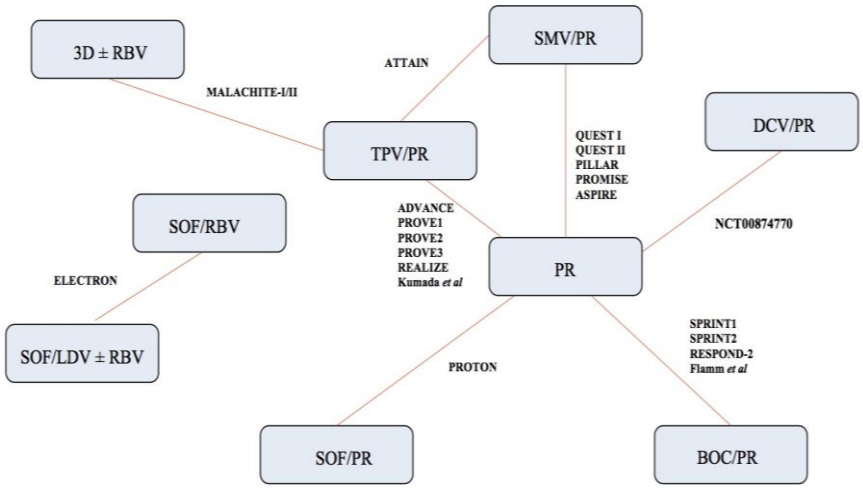


Figure 40: Network diagram of randomised controlled trials included in the analysis
The red line indicates the connection between the two treatment regimens. The RCT(s) that connect the two regimens are listed beside each connecting line.

Figure 41 presents the cumulative rankogram and illustrates the probability that each drug combination is the n^{th} best treatment. 3D±RBV had a probability greater than 0.9 of being the 1st ranked treatment regimen in the RCT-only NMA.

The normalised SUCRA for the RCT-only NMA model indicated that 3D±RBV had the largest proportion under the cumulative rankogram curve (25%) and thus, had the highest probability of being the most effective treatment compared to PR (Table 45).

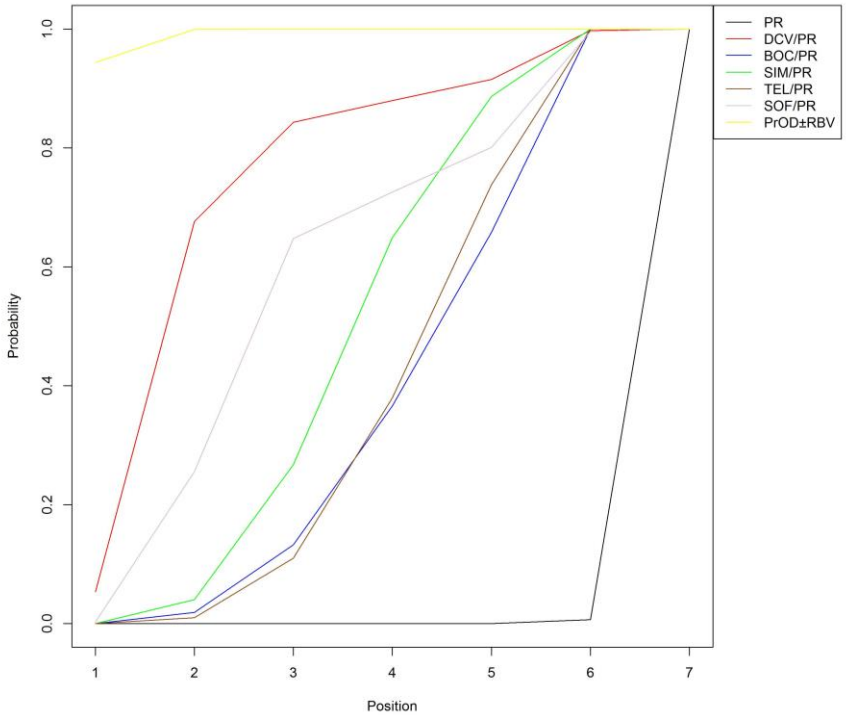


Figure 41: Cumulative rankogram for RCT evidence only

Table 45: SUCRA Table for RCT only network meta-analysis

	3D±RBV	DCV/PR	SOF/PR	SMV/PR	BOC/PR	TPV/PR	PR
SUCRA	25%	20%	16%	14%	11%	11%	2%

The model was re-run to include both the 20 RCTs and the 23 single-agent, non-comparative clinical studies. The network was connected as per the methods assessed by Leahy *et al* [407]. Pooled and hierarchical models were used to assess the relative treatment effect. Figure 42 illustrates the network diagram after connecting all 43 studies.

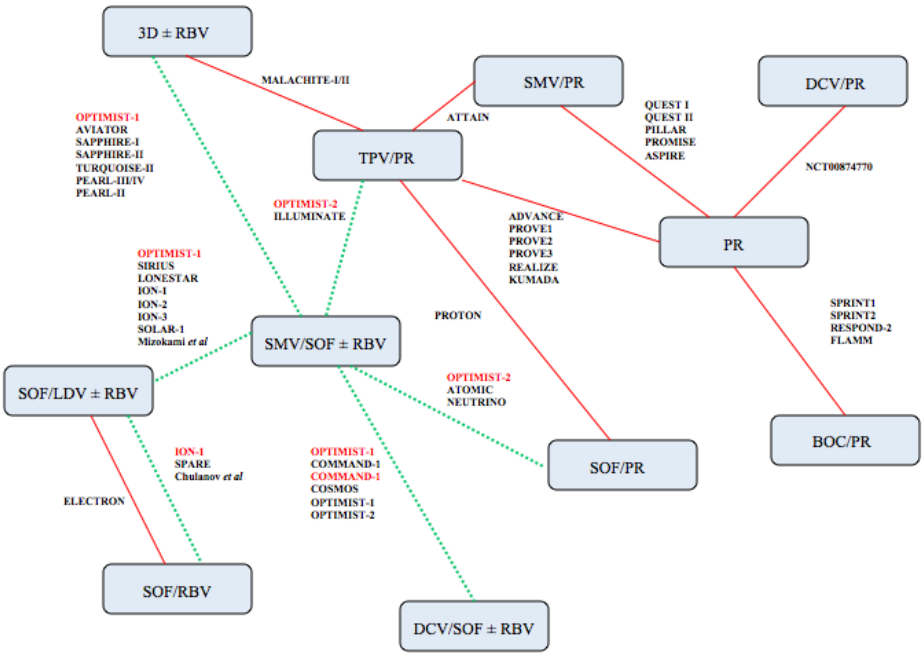


Figure 42: Network diagram for both the pooled and hierarchical models
This diagram represented the connected network and is a combination of the RCT-only network and the non-comparative studies. The red lines indicate the RCT trials and the green dashed indicates the single-agent studies

Figure 43 presents the cumulative rankograms for the pooled and hierarchical models and illustrates the probability that each drug combination is the n^{th} best treatment. In Figures 43 and Figure 44, we can see that 3D±RBV has a probability greater than 0.4 and 0.45 of being the 1st ranked treatment regimen in the pooled and hierarchical models, respectively.

The normalised SUCRA score for both the pooled and hierarchical models indicated that 3D±RBV had the largest proportion under the cumulative rankogram curves (16% and 16%, respectively) and thus had the highest probability of being the most effective treatment compared to PR.

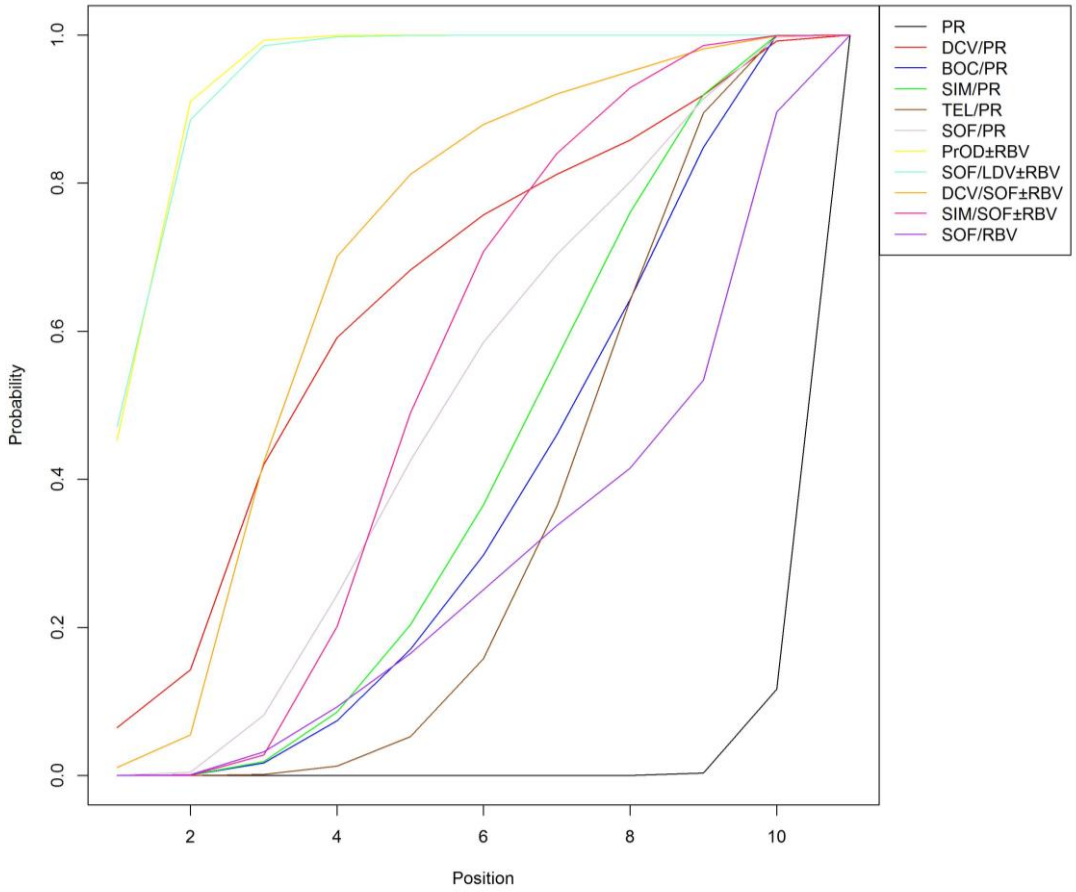


Figure 43: The cumulative rankogram for the pooled model – excluding observational studies

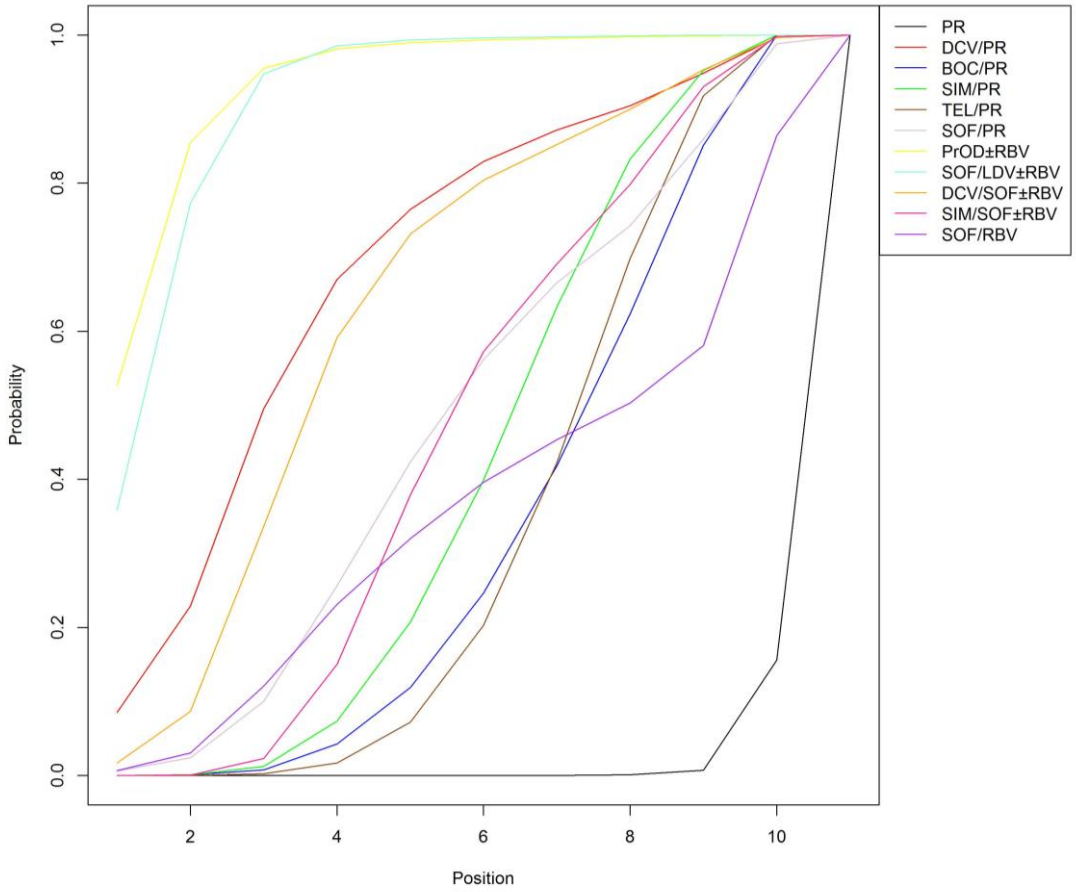


Figure 44: The cumulative rankogram for the hierarchical model – excluding observational studies

8.2.2.2 Clinical Trials and Observational Studies

In addition to the RCTs and single-agent non-comparative trials, the systematic review identified 43 observational studies. There was insufficient data on the proportion of patients with cirrhosis in fourteen studies, a characteristic required by Leahy *et al* to connect the networks [407]; therefore, 29 of these observational studies, with and without comparator groups, were included in this analysis. Overall, 20 RCTs with a comparator group, 23 non-comparative single-agent clinical trials, 16 observational studies that included more than one treatment arm and 13 single-agent observational studies were included. Figure 45 illustrates the network diagram of the pooled model for the entire connected network following the inclusion of the observational studies.

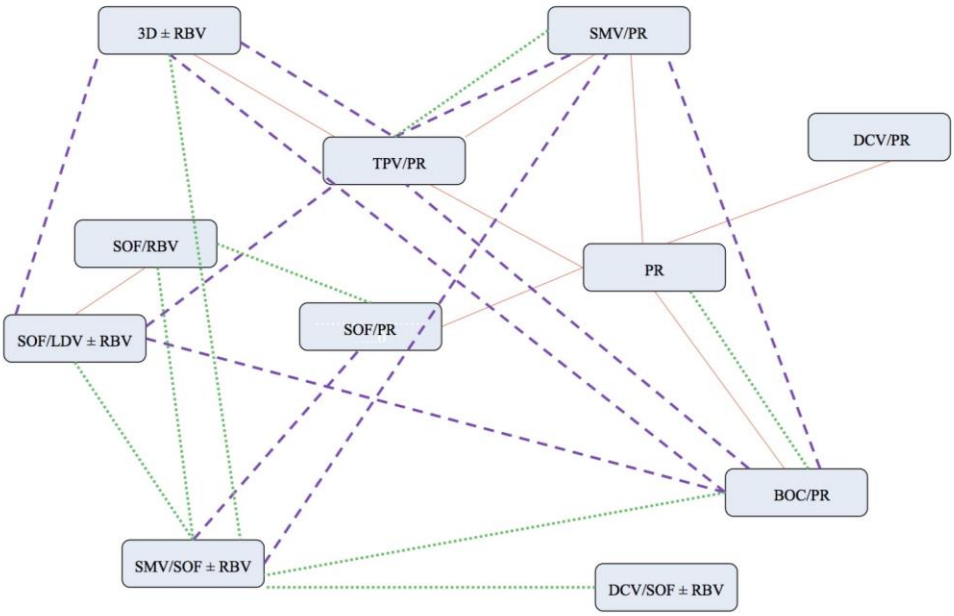


Figure 45: Network diagram for the pooled model
This diagram represented the connected network and is a combination of the RCTs, the observational comparator studies and the non-comparative trials. The red lines indicate the RCT trials, the purple dashed lines indicate the observational comparator studies and the green dashed indicates the single-agent studies.

For the hierarchical model, adjustments to the matching were required in order to form a connected network. Figure 46 illustrates the network diagram for the hierarchical model of the entire connected network.

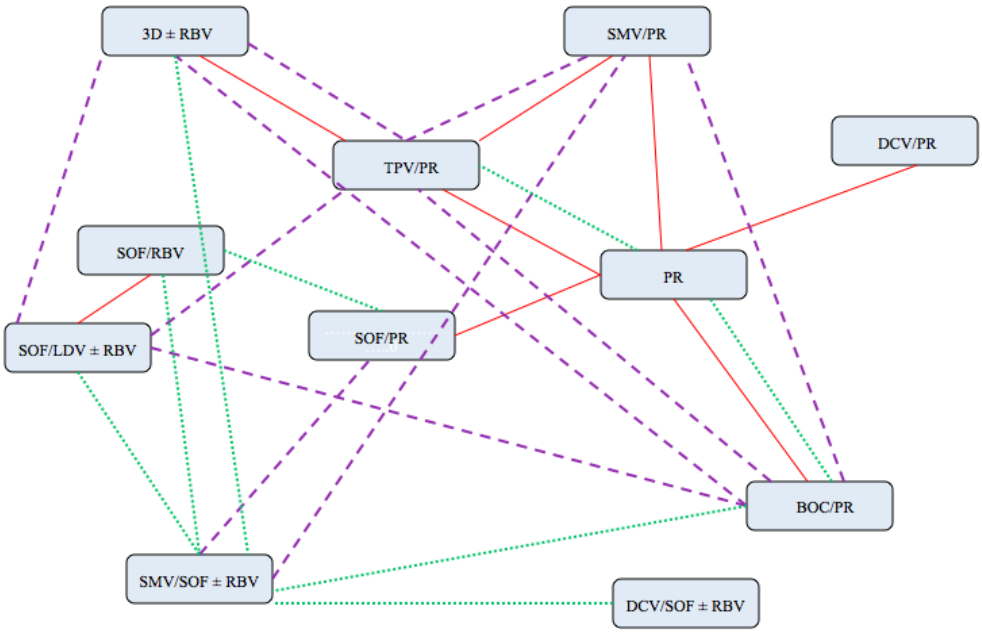


Figure 46: Network diagram for the hierarchical model
This diagram represented the connected network and is a combination of the RCT, the observational comparator studies and the matched single-agent studies. The red lines indicate the RCT trials, the purple dashed lines indicate the observational comparator studies and the green dashed indicates the single-agent studies.

The cumulative rankograms illustrated the probability that each drug combination is the n^{th} best treatment (Figure 47). In Figure 47 and Figure 48, we can see that 3D±RBV had a probability greater than 0.8 and 0.75 of being the 1st ranked treatment regimen in the pooled and hierarchical models, respectively.

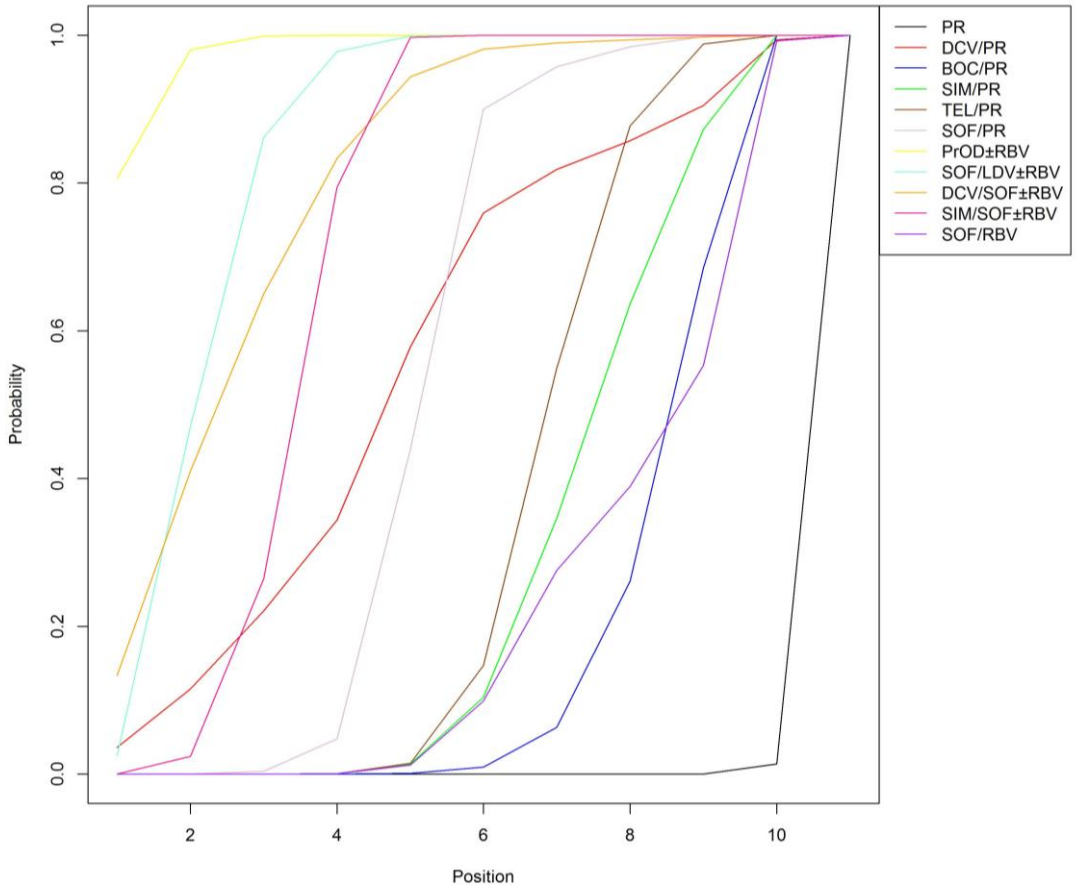


Figure 47: The cumulative rankogram for the pooled model – including observational studies

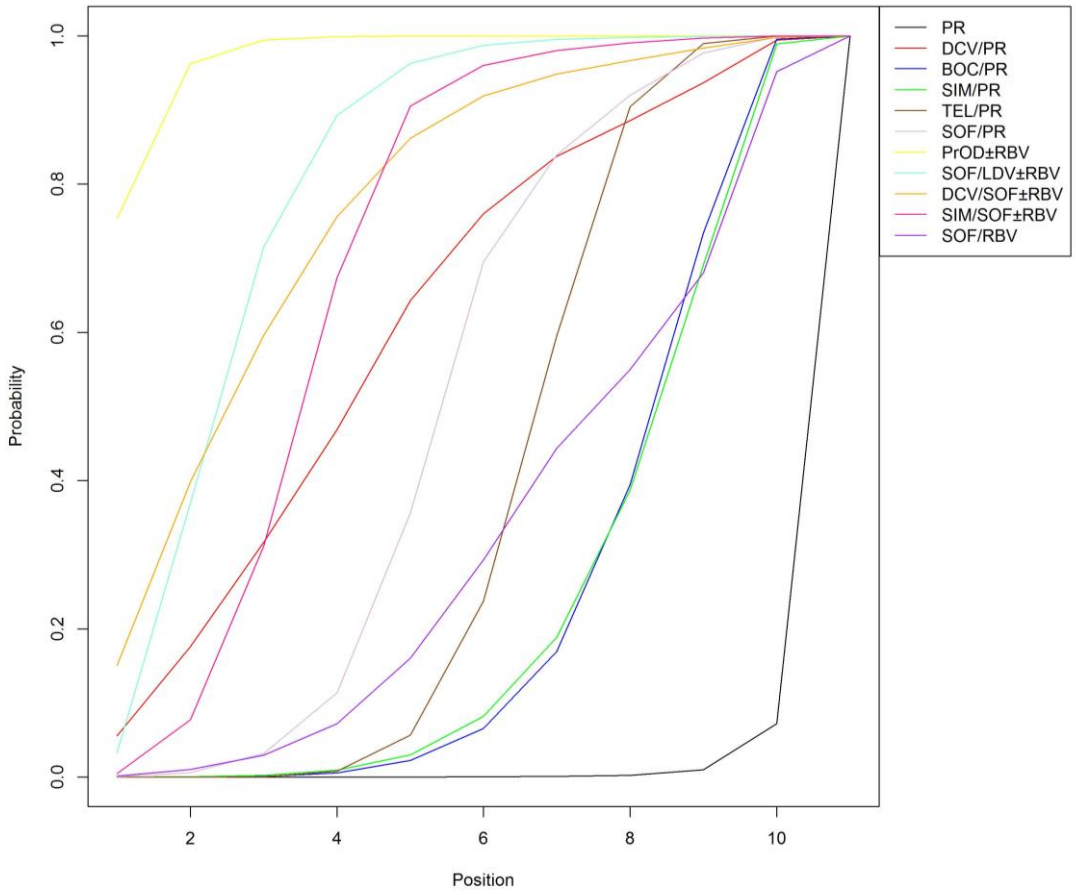


Figure 48: The cumulative rankogram for the hierarchical model – including observational data

The normalised SUCRA score for both the pooled and hierarchical models indicated that 3D±RBV had the largest proportion under the cumulative rankogram curves (16% and 16%, respectively) and thus had the highest probability of being the most effective treatment compared to PR.

Given the inherent bias that is associated with observational studies, an additional model was run whereby the observational data in the hierarchical model was down-weighted to adjust for this bias. In **Error! Reference source not found.**, we see that 3D±RBV had a probability of approximately 0.8 of being the 1st ranked treatment regimen in the hierarchical model when the observational data is down-weighted. The normalised SUCRA score indicated that 3D±RBV had the largest proportion under the

cumulative rankogram curves (16%) and thus had the highest probability of being the most effective treatment compared to PR.

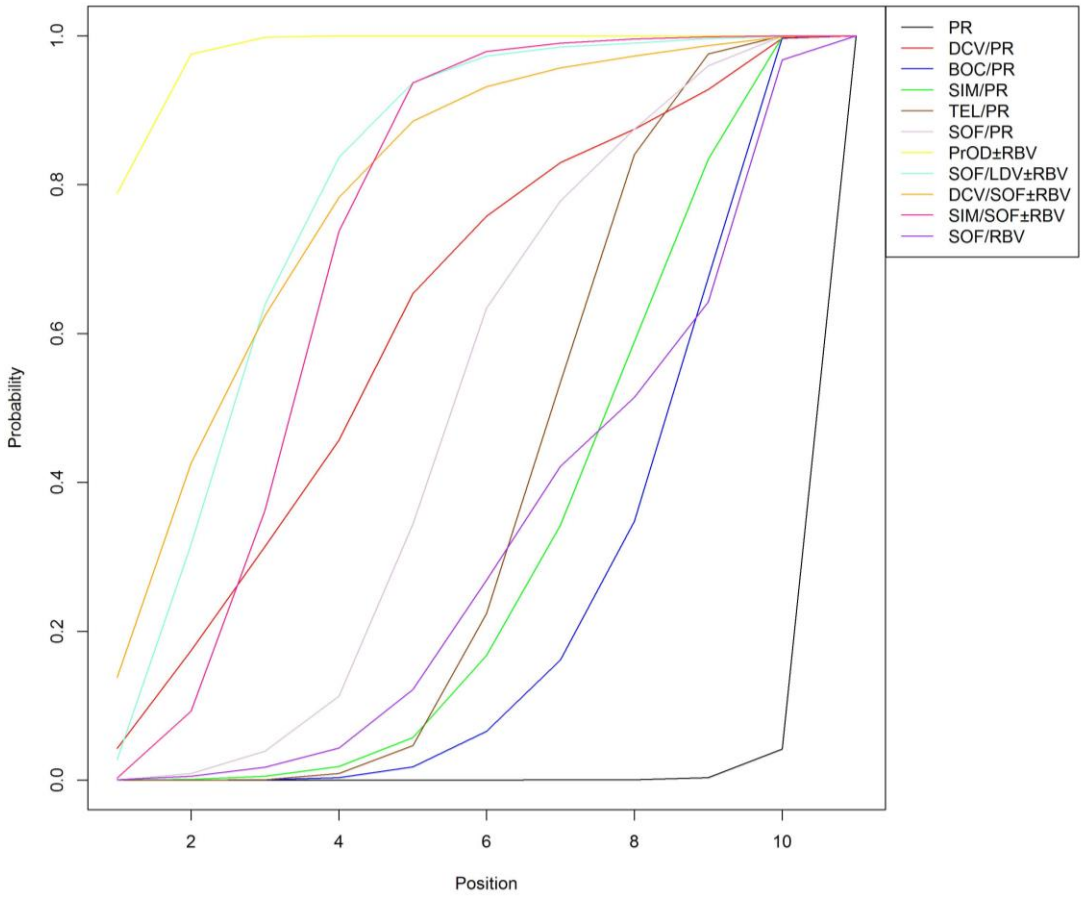


Figure 49: The cumulative rankogram for the down-weighted hierarchical models – including observational data

8.2.2.3 Log Odds Ratio

The LOR for each treatment regimen versus PR was determined. The LOR of SVR in DAA regimens was statistically significantly greater than the LOR of SVR in PR only. There were a few exceptions where no statistical significance was observed (Appendix 4 Table A 15 − Table A 20). In all models presented, the LOR of SVR after treatment with 3D±RBV versus PR was greatest. This was followed by DCV/PR in the RCT-only model but in the models that incorporated all evidence, the LOR of SVR for SOF/LDV±RBV versus PR was the second highest.

Figure 50 shows the LOR for each drug versus PR when the observational studies were excluded. The LOR of SVR in 3D±RBV was 4.23 (CrI 3.18-5.32), 3.84 (CrI 2.71-4.95) and 3.76 (CrI 2.15-5.02) for the RCT-only, pooled and hierarchical models, respectively. The CrI for SOF+RBV in the hierarchical model spanned 0 and therefore, we conclude that the log odds of SVR for this regimen is not statistically significantly better than PR.

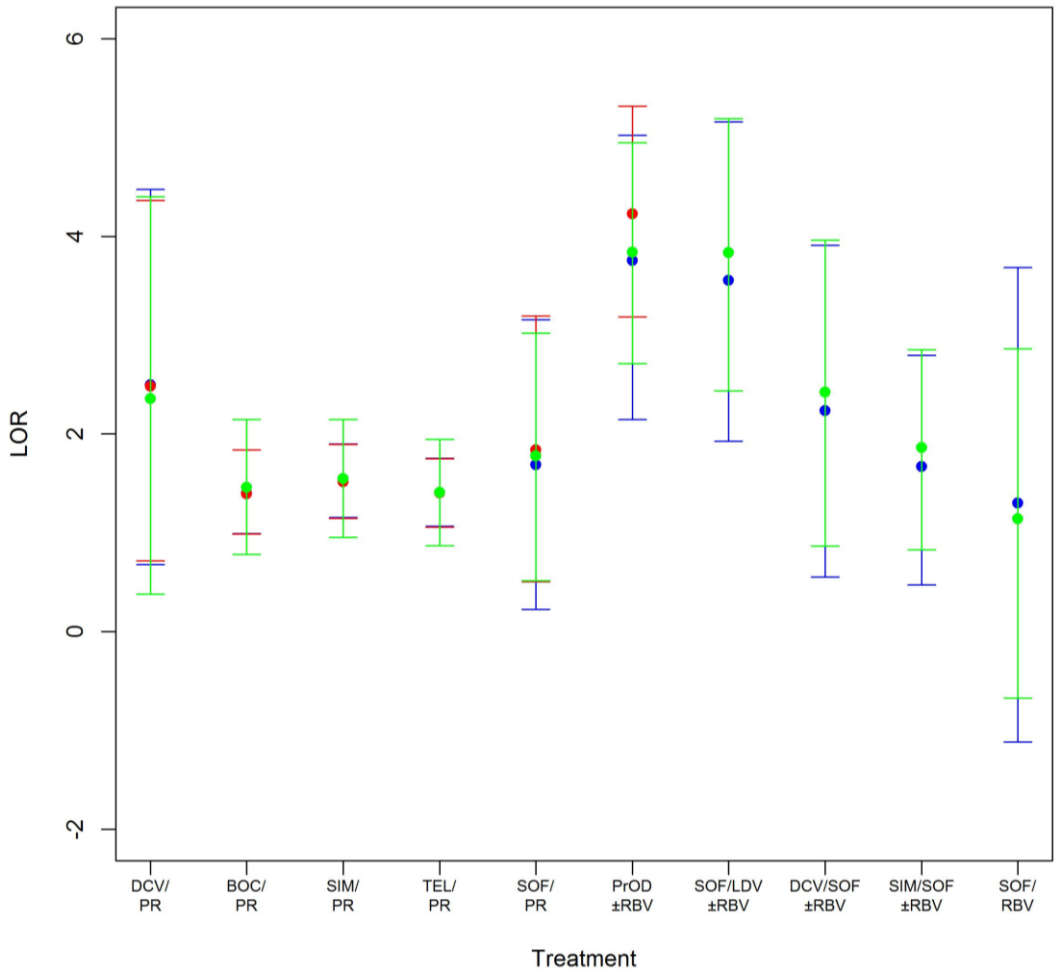


Figure 50: Log odds ratio of achieving a SVR vs. PR for the RCTs-only, pooled and hierarchical models.
Observational studies were excluded from this analysis. The LOR and CrIs for the RCT-only model are marked in red, green for the pooled model and blue for the hierarchical model.

Figure 51 shows the log odds ratio for each drug versus PR when the observational studies were included. The LOR of SVR in 3D±RBV was 4.4 (CrI 3.6-5.22), 4.27 (CrI 3.01-5.51) and 4.36 (CrI 2.94-5.1) for the pooled, hierarchical and hierarchical with down-weighted observational data models, respectively. In this scenario, the CrIs for

SOF+RBV in the both hierarchical models spanned 0 and therefore, we conclude that in these models the log odds of SVR for SOF+RBV is not statistically significantly better than PR. For all treatment regimens in the pooled model, the standard deviations of estimates become smaller when the observational data was included. In the hierarchical model, the standard deviation of estimates varies when observational data was included. For some treatment regimens, the standard deviation increases (DCV/PR, BOC/PR, SMV/PR, TPV/PR, SOF/DCV±RBV and SOF/SMV±RBV) and for others it decreases (SOF/PR, 3D±RBV, DCV/SOF±RBV and SOF+RBV). This is likely caused by the fact that this model type allows for uncertainty caused by combining evidence from different trial designs. After down-weighting the observational data, similar changes in standard deviations are observed but the CrIs became narrower suggesting some decrease in uncertainty surrounding the estimates.

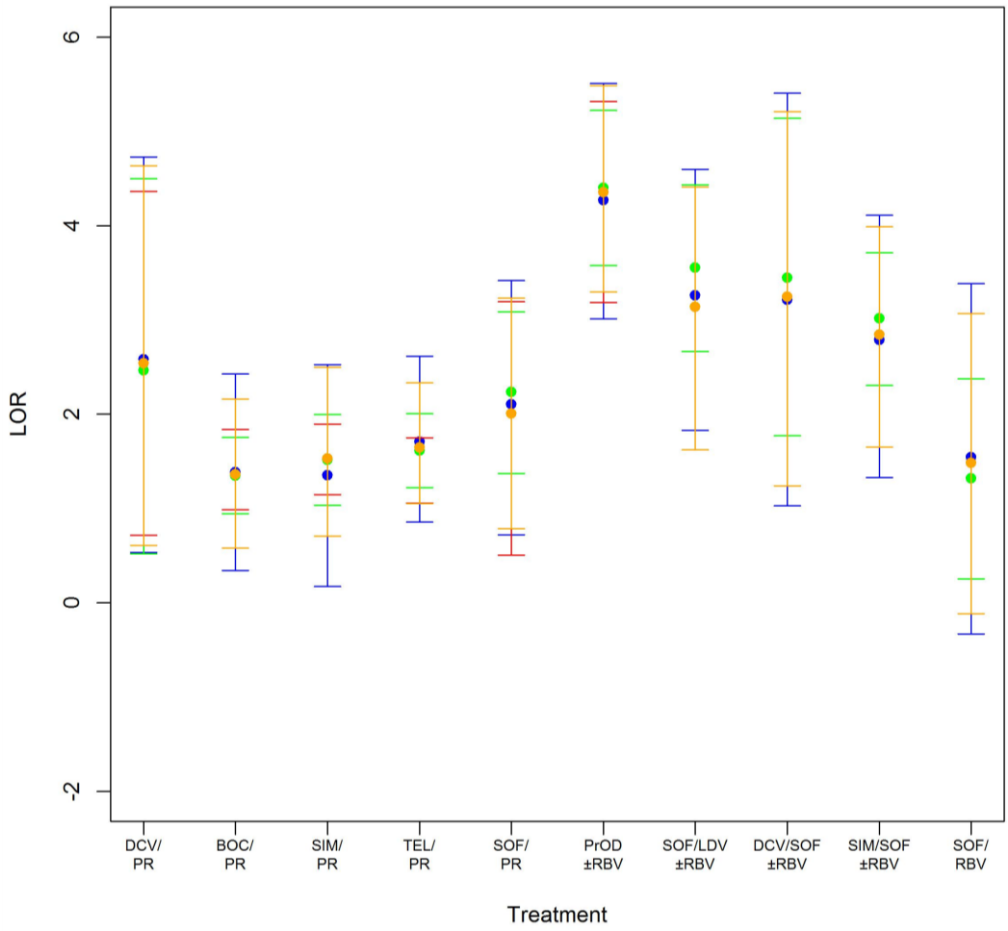


Figure 51: Log odds ratio of achieving a SVR vs. PR for the RCTs-only, pooled, hierarchical models and down-weighted hierarchical model.
Observational studies were included in these models. The LOR and CrIs for the RCT-only model are marked in red, for the pooled model are marked in green, for the hierarchical model are marked in blue and for the hierarchical model with observational data down-weighted are marked in orange

8.2.2.4 Treatment Ranking

Table 46 presents the ranking of each treatment regimen in each model reported in this analysis. Overall, 3D±RBV was the 1st ranked and SOF/LDV±RBV was the 2nd ranked treatment versus PR in each model-type, with the exception of the RCT-only model, which did not include SOF/LDV±RBV. Every treatment regimen performed better than PR. DCV/SOF±RBV was the 3rd ranked treatment in all models with the exception of the hierarchical model where it ranked 4th behind SOF/DCV±RBV. The IFN-free regimens ranked higher than the IFN-based regimens, with the exception of SOF+RBV, which was consistently ranked as one of the least effective treatment regimens in this GT1 HCV-infected cohort.

Table 46: Treatment ranking for each model variation

	RCT only	Pooled Excl. obs studies	Hierarchical Excl. obs studies	Pooled Incl. obs studies	Hierarchical Incl. obs studies	Hierarchical Incl. down-weighted obs studies
3D±RBV	1	1	1	1	1	1
SOF/LDV±RBV	-	2	2	2	2	2
DCV/SOF±RBV	-	3	4	3	3	3
SOF/SMV±RBV	-	5	6	4	4	4
DCV/PR	2	4	3	5	5	5
SOF/PR	3	6	5	6	6	6
SMV/PR	4	7	7	8	10	8
BOC/PR	6	8	10	10	9	10
TPV/PR	5	9	9	7	7	7
SOF+RBV	-	10	8	9	8	9
PR	7	11	11	11	11	11

8.2.3 Discussion

This study estimated the relative treatment effect of licensed regimens for the treatment of HCV GT1-infected patients following the inclusion of observational data. 3D±RBV was consistently ranked as the most effective treatment in GT1-infected patients, closely followed by SOF/LDV±RBV, irrespective of whether observational studies were included in the model or not. Overall, the clinical effectiveness of the IFN-free regimens was better than the IFN-based regimens with the exception of SOF+RBV, which was frequently one of the lowest ranked treatments.

While large, well-conducted clinical trials can provide high-quality evidence for informing decisions to license and reimburse new agents, open-label, single-agent, non-comparative studies and observational studies can play an integral role when evaluating treatment effect [11-13, 161, 408]. For HCV, many of the clinical trials deemed appropriate for regulatory approval lack a treatment arm involving placebo or an accepted standard of care. This has become more common with the introduction of the BTD by the FDA where therapies that demonstrate substantial improvements on outcomes over existing therapies are not required to have a comparator treatment arm [282, 357, 409]. There are important challenges associated with the use of single-arm trials.

In these, all enrolled subjects receive the intervention and there is no comparator arm. While advantageous because of the low expected sample size, the lack of randomisation means that causal interpretation is not possible – selection bias can lead to a biased treatment effect and a lack of confidence in a positive result [410]. Single-arm trials differ from observational studies in the absence of treatment assignment. In observational studies, the physician chooses the treatment option that is believed to be best for the patient whereas, in the single-arm trials, all subject are treated with the one intervention under investigation.

With the increasing number of non-comparative studies, decision-makers may lack the evidence required (comparator/placebo-controlled studies) to derive estimates of relative effect due to the 'disconnected' evidence base. While other studies have examined approaches for forming connected networks through the incorporation of single-arm evidence, we assessed the impact of including observational evidence into these networks [407, 409, 411].

One of the incentives for combining evidence from different sources is to make an informed decision on the basis of all the available evidence. However, although observational studies reflect reality well, they can be prone to bias leading to an overestimation of the treatment effect. While the inclusion of RCTs exclusively in the NMAs may be the most internally valid approach, we can argue that it is a suboptimal approach given that data from alternative study designs, such as single-agent, non-comparative studies and observational studies contain further information about treatment effect.

In this study, we found that the addition of observational data did not impact the treatment ranking. 3D±RBV, SOF/LDV±RBV and DCV/SOF±RBV were the first three ranked treatments with the exception of the hierarchical model excluding observational data, where DCV/PR was the 3rd ranked treatment. For the majority of treatments, the LOR were slightly higher after the inclusion of observational evidence.

The impact of incorporating observational evidence into different model types was also assessed. In the pooled models, when observational data were added to the RCTs and single-agent, non-comparative clinical trials, standard deviations decreased, indicating that the addition of further data in the form of the observational studies strengthened the evidence. However, pooled models make the strong assumptions of homogeneity in trial design and thus, does not allow for bias adjustments and no additional uncertainty was taken into account. Therefore, the observational data was treated in the same manner as the clinical trial data, and the additional bias associated with observational data was not considered. As a result, this type of naïve pooling has not been recommended as a primary means of combining evidence from different study designs [267]. In the hierarchical models, which are the most flexible approach for including different forms of evidence and account for between study design heterogeneity, the impact of including observational data was assessed with and without down-weighting to adjust for the associated bias. The addition of observational data resulted in standard deviations increasing and decreasing depending on the treatment regimen. After down-weighting the observational data, similar changes in standard deviations are observed but the CrIs indicated a decrease in uncertainty surrounding the estimates.

In HCV research, there are many observational studies available providing additional data on treatment effectiveness. It is important that decision-makers consider all

available evidence. At the time of the initial reimbursement decision, available evidence tends to be immature, that is, there is still potential that further evidence, in particular real world evidence, will become available in time. Therefore, this would suggest that the introduction of a conditional reimbursement scheme would ensure that final decisions made by payers are informed by a combination of RCT and real world evidence.

The findings indicate that the inclusion of observational studies has the potential to improving the accuracy in the estimation of the relative treatment effect. This was demonstrated by the decreasing standard deviations observed after incorporating observational studies into the pooled model. Given that a similar effect was not observed in the hierarchical model, this would suggest that more research is required to ensure that the observational studies are incorporated appropriately, the associated bias is considered and studies are down-weighted accordingly.

At present, it is important to interpret the results from this NMA with care as there is still uncertainty surrounding the best and most reliable approaches for connecting the networks and incorporating different types of evidence into the models. However, under the correct circumstances, the addition of observational evidence to the NMA is likely to produce more accurate estimates of relative treatment effect, which will be highly valuable in the HTA process.

8.3 Part 2: Real World Cost-Effectiveness Model

8.3.1 Methods

We applied the rates of clinical effectiveness and on-treatment HCV-related costs for TPV/PR and BOC/PR established in this research project to an independently produced economic model developed by a colleague in the NCPE for a previous PhD thesis[††]. A hybrid model, which combined an initial decision tree structure examining different treatment strategies with a Markov model which examines costs and outcomes over a longer term, was built using TreeAge© software. The decision tree and Markov model are presented graphically in Figure 52 and Figure 53, respectively.

[††] This economic model was developed by Dr. Jennifer Kieran of the National Centre for Pharmacoeconomics for her PhD thesis 'The Cost-Effectiveness of Hepatitis C Treatments in Ireland: A Multi-Technology Assessment'. This was the first independent produced model in Ireland to directly compare the cost-utility of treatment with boceprevir and telaprevir and the first to evaluate the cost-effectiveness of pegylated-interferon and ribavirin therapy.

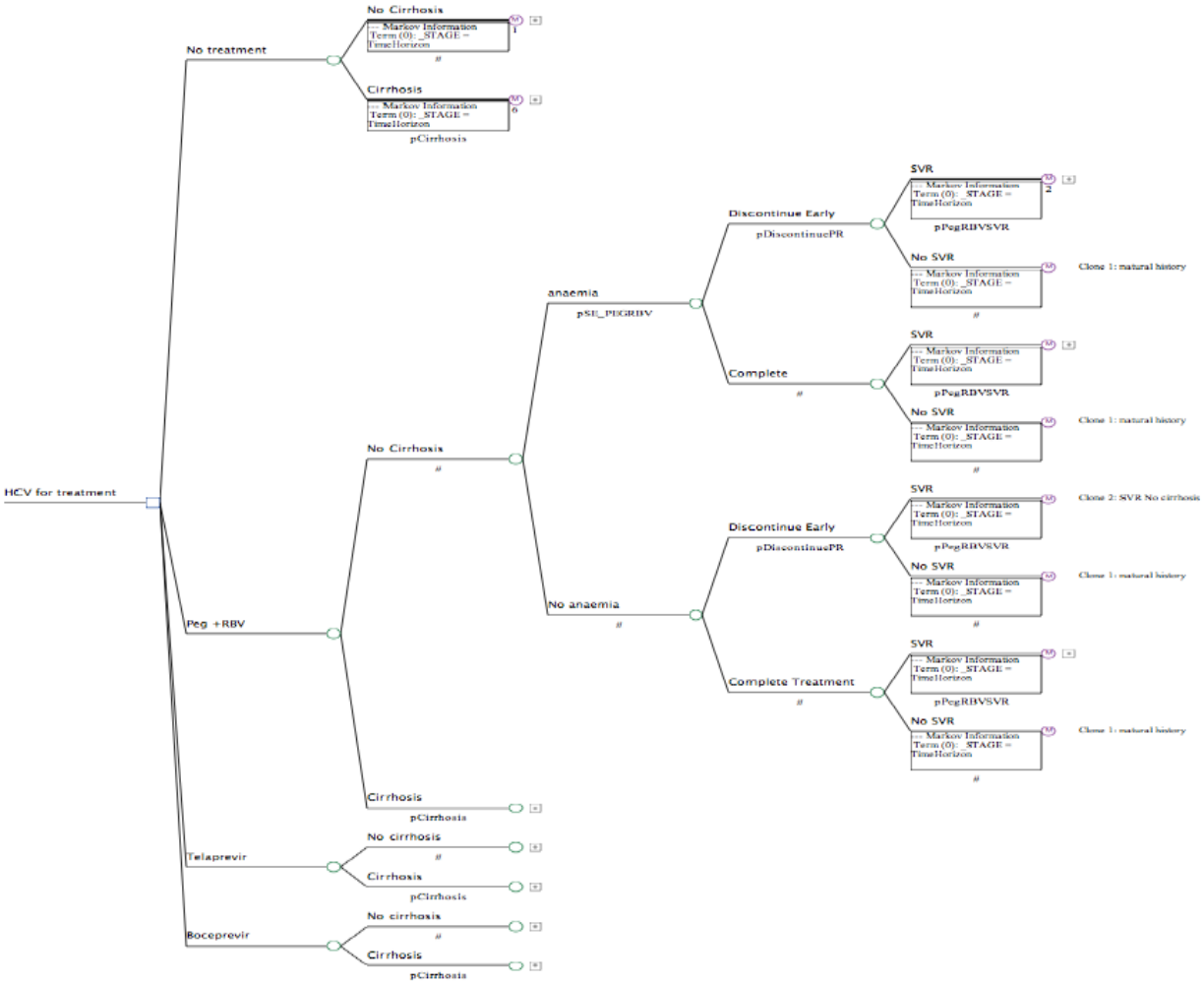


Figure 52: Outline of the decision tree

Sourced from Kieran J [412]

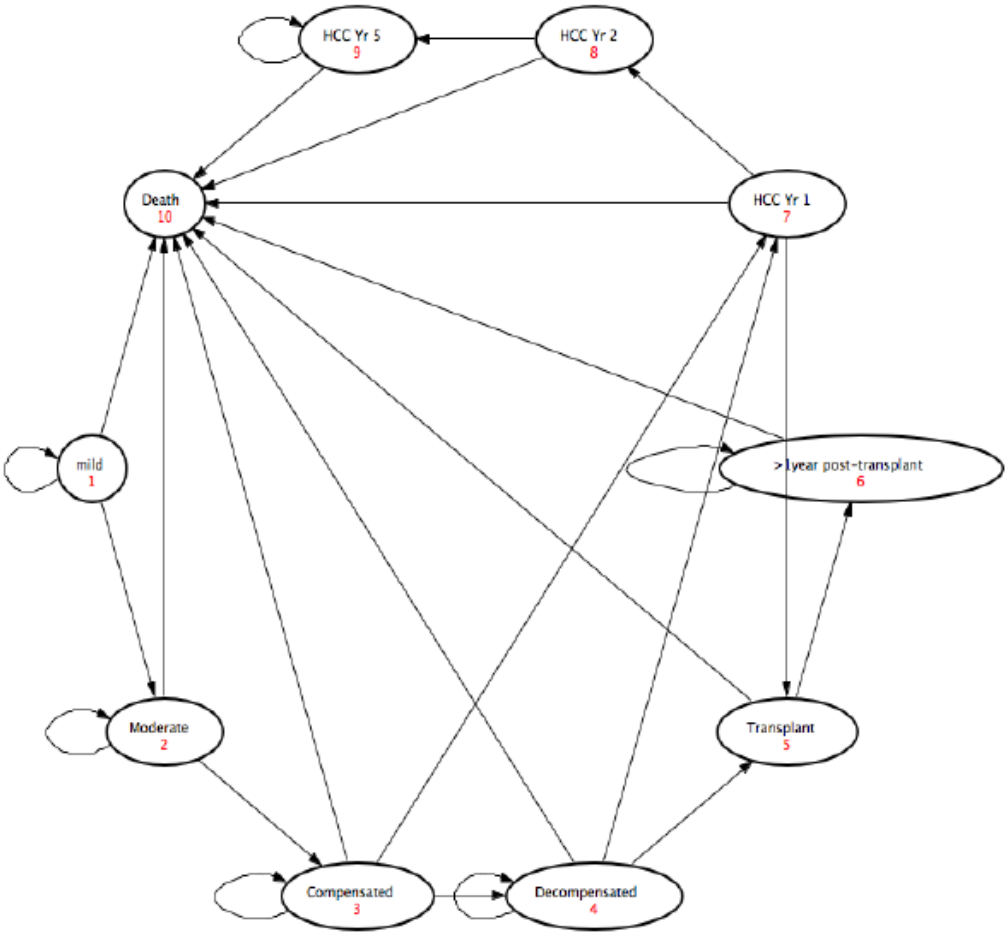


Figure 53: Outline of the Markov model for HCV

Sourced from Kieran J [412]

The model was designed to consider treatment options for HCV infection approved for reimbursement in Ireland in August 2014. These included PR for 48 weeks and triple therapy with either TPV/PR or BOC/PR. The option of no treatment was also included as a comparator as this was the standard of care for patients who were ineligible for, or unable to tolerate IFN-based regimens.

The rates of clinical effectiveness established in Chapter 5 in this thesis were applied to the model. The HCV drug costs, the on-treatment monitoring costs and the costs of managing adverse events derived from the micro-costing study in Chapter 6 were also

applied as inputs into the model. Given the availability of our individual patient level data, we were able to determine more specific effectiveness and cost data within the cirrhotic and non-cirrhotic subgroups than was possible in the original analysis where data was derived from clinical trials and published literature. Access to on-treatment HCV-RNA data allowed us to calculate the probability of patients achieving a rapid virological response (RVR) which was an important for determinant for treatment duration. Table 47 and Table 48 present the inputs for treatment efficacy used in the original analysis by NCPE colleagues and the inputs for clinical effectiveness applied to this analysis using data from studies in this thesis, respectively. As a result of our patient level data, Table 48 is populated with more specific population data than in Table 47.

Table 47: Treatment efficacy probabilities, obtained from RCTs and published literature, used in the initial NCPE analysis

Parameter	**NCPE Analysis *(2014)***
Probability of SVR in non-cirrhotics	0.41
Probability of SVR in cirrhotics	0.3
Relative efficacy of Telaprevir	1.69
Relative efficacy of Boceprevir	1.66
Probability of SVR in Telaprevir (no cirrhosis)	0.69
Probability of SVR in Telaprevir (cirrhosis)	0.51
Probability of SVR in Boceprevir (no cirrhosis)	0.68
Probability of SVR in Boceprevir (cirrhosis)	0.5

Table 48: Treatment effectiveness probabilities used in the analysis, which incorporated the real world data from this thesis

Parameter	Real World Analysis *(2016)*
Non-cirrhotic Cohort	
Probability of SVR in Boceprevir with a RVR	0.89
Probability of SVR in Boceprevir without a RVR	1
Probability of SVR if discontinued Boceprevir early and achieved a RVR	0.17
Probability of SVR if discontinued Boceprevir early and did not achieved a RVR	0.2
Probability of receiving EPO in Boceprevir	0.36
Probability of SVR in Telaprevir with a RVR	0.95
Probability of SVR in Telaprevir without a RVR	0.95
Probability of discontinuing Telaprevir with a RVR	0.27
Probability of discontinuing Telaprevir without a RVR	0.22
Probability of SVR if discontinued Telaprevir early and achieved a RVR	0.17
Probability of SVR if discontinued Telaprevir early and did not achieved a RVR	0.29
Probability of receiving EPO in Telaprevir	0.38
Cirrhotic Cohort	
Probability of SVR in Boceprevir (cirrhosis)	0.75
Probability of discontinuing Boceprevir (cirrhosis)	0.69
Mean no. of weeks of treatment with Boceprevir before discontinuing (cirrhosis)	22
Probability of anaemia in Boceprevir (cirrhosis)	0.54
Probability of receiving EPO in Boceprevir (cirrhosis)	0.57
Probability of SVR in Telaprevir (cirrhosis)	0.89
Probability of discontinuing Telaprevir (cirrhosis)	0.32
Mean no. of weeks of treatment with Telaprevir before discontinuing (cirrhosis)	11.5
Probability of SVR if discontinued Telaprevir early (cirrhosis)	0
Probability of anaemia in Telaprevir (cirrhosis)	0.36
Probability of receiving EPO in Telaprevir (cirrhosis)	0.7

These probabilities were derived from the studies undertaken in Chapters 5.
RVR = Rapid virological response

Table 49 and Table 50 present the cost inputs used in the original model (NCPE) and those applied for this analysis based on the costs derived from the micro-costing study in *Chapter 6*, respectively. In the original analysis, the cost of HCV-drugs, cost of monitoring and post-treatment monitoring costs were all incorporated separately, having been identified in the literature. In Chapter 6, we determined a total cost of treatment per patient which included the cost of HCV-drugs, the cost of monitoring, of treating adverse events and the post-treatment period to SVR24 in the one calculation. Additionally, our HCV-RNA data enabled us to specify cost in patients who achieved, and did not achieve, a RVR.

Table 49: Cost inputs for drugs and on-treatment monitoring used in the analysis by the NCPE

Parameter	Cost
Cost of TPV (12 weeks)	€26,334
Cost of BOC (24 weeks)	€19,333
Cost of BOC (32 weeks)	€25,777
Cost of BOC (44 weeks)	€35,444
Cost of PR (24 weeks)	€7,773
Cost of PR (28 weeks)	€9,096
Cost of PR (48 weeks)	€15,547
On-treatment monitoring (24 weeks)	€2,738
On-treatment monitoring (28 weeks)	€2,916
On-treatment monitoring (48 weeks)	€3,856
Cost of post-treatment monitoring	€708
Cost of course of erythropoietin	€4,728
Cost of baseline HCV workup	€1,523

The inputs for this analysis were derived from medication list prices and two studies published by Kieran et al; a micro-costing study to assess the costs of untreated HCV and a study determining the budget impact of HCV in Ireland in the pre-DAA era [81, 82]

Table 50: Cost inputs for drugs and on-treatment monitoring derived from the micro-costing study in this thesis that were incorporated into the model

Parameter	Cost
Cost of Telaprevir treatment, on-treatment monitoring and post-treatment monitoring (24 weeks)	€38,825
Cost of Telaprevir treatment, on-treatment monitoring and post-treatment monitoring (48 weeks)	€47,430
Cost of Boceprevir treatment, on-treatment monitoring and post-treatment monitoring (24 weeks)	€33,661
Cost of Boceprevir treatment, on-treatment monitoring and post-treatment monitoring (32 weeks)	€45,738
Cost of Boceprevir treatment, on-treatment monitoring and post-treatment monitoring (48 weeks)	€54,799
Cost of treating anaemia in Telaprevir with a RVR	€747
Cost of treating anaemia in Telaprevir without a RVR	€1,888
Cost of treating anaemia in Boceprevir with a RVR	€1,719
Cost of treating anaemia in Boceprevir without a RVR	€7,643
Cost of baseline HCV workup	€608

These probabilities were derived from the studies undertaken in Chapters 6.
RVR = Rapid virological response

Based on the demographics of the cohort treated with TPV/PR and BOC/PR, patients entered the model with a starting age of 48 years. This compared with a starting age of 41 years in the initial model, which was based on data from a study by Kieran *et al* published in 2015 [82]. The time horizon in the model developed by the NCPE was 50 years based on an expected life-time of 90 years. With the change in starting age from 41 years to 48 years in this analysis, the time horizon was adjusted to 40 years.

Deterministic analysis was undertaken. This involved the calculation of a mean value for the variable of interest (ICER). The NCPE model examined the expected life-time costs and QALY gains of the considered treatments under a base case scenario, which

consisted of a population of 80% non-cirrhotic and 20% cirrhotic patients with HCV infection. In separate scenario analyses, the model was re-run to examine the impact of having either a 100% non-cirrhotic or a 100% cirrhotic cohort. Using real world inputs, the base case scenarios consisted of a population of 65% non-cirrhotic and 35% cirrhotic HCV patients to reflect the cohort from which the real world inputs were derived. Additionally, we examined the impact of having a 100% non-cirrhotic and 100% cirrhotic cohort.

8.3.2 Results

8.3.2.1 Base Case Population

In the base case scenario, TPV/PR was considered the most cost-effective treatment of the four strategies (No treatment, PR, BOC/PR and TPV/PR) with an ICER of €28,880 when compared with PR, which is below the current WTP threshold of €45,000 in Ireland (Table 51). BOC/PR was subject to extended dominance i.e. the ICER was greater than that of TPV/PR, which is a more effective intervention.

Table 51: Life-time costs, QALY and incremental cost-effectiveness ratios for the base case scenario

Strategy	Cost	Effectiveness (QALY)	Incremental Cost	Incremental Effectiveness	ICER
No treatment	€27,252	9.97			
PR	€38,056	10.58	€10,804	0.61	€17,649
TPV/PR	€58,434	11.29	€20,378	0.71	€28,880

This outcome contrasted with the base case scenario from the NCPE analysis whereby, BOC/PR was considered the most cost-effective option under the WTP threshold with an ICER of €24,233. None of the treatment strategies were dominated in that analysis, although the ICER generated for TPV/PR versus BOC/PR (€128,082) was above the Irish WTP threshold. Figure 54 illustrates the cost-effectiveness plane for the base case in this analysis.

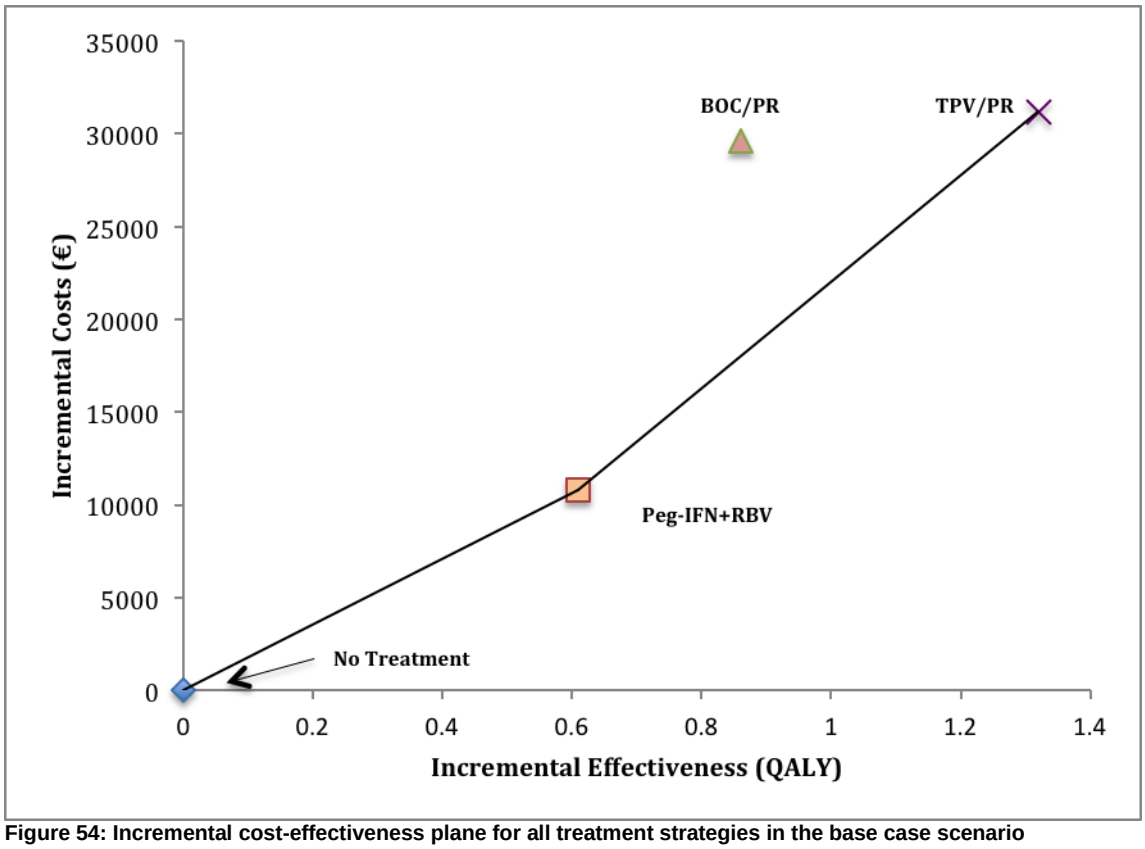


Figure 54: Incremental cost-effectiveness plane for all treatment strategies in the base case scenario
The line between No Treatment and Peg-IFN/PR and Peg-IFN/PR and TPV/PR represents the cost-efficiency frontier. The frontier represents the most efficient choices among compared treatment strategies. Compared with Peg-IFN+RBV, TPV/PR is the most efficient strategy. Any point not on this frontier is dominated, either by strict of extended dominance. BOC/PR is subject to extended dominance..

8.3.2.2 100% Non-Cirrhotic Population

In the scenario considering only patients with mild to moderate HCV at baseline (100% non-cirrhotic), the life-time costs are lower than the base case and the QALY gains are higher for all strategies. TPV/PR was the preferred agent with an ICER of €39,610 compared with PR which was below the WTP threshold (Table 52).

Table 52: Life-time costs, QALY and incremental cost-effectiveness ratios in a cohort with mild/moderate HCV infection

Strategy	Cost	Effectiveness (QALY)	Incremental Cost	Incremental Effectiveness	ICER
No treatment	€12,168	12.15			
PR	€24,844	12.65	€12,658	0.5	€25,196
TPV/PR	€45,076	13.16	€20,232	0.51	€39,610

Similar to the base case, BOC/PR was subject to extended dominance. The life-time costs, clinical effectiveness and ICERs are presented in Figure 55.

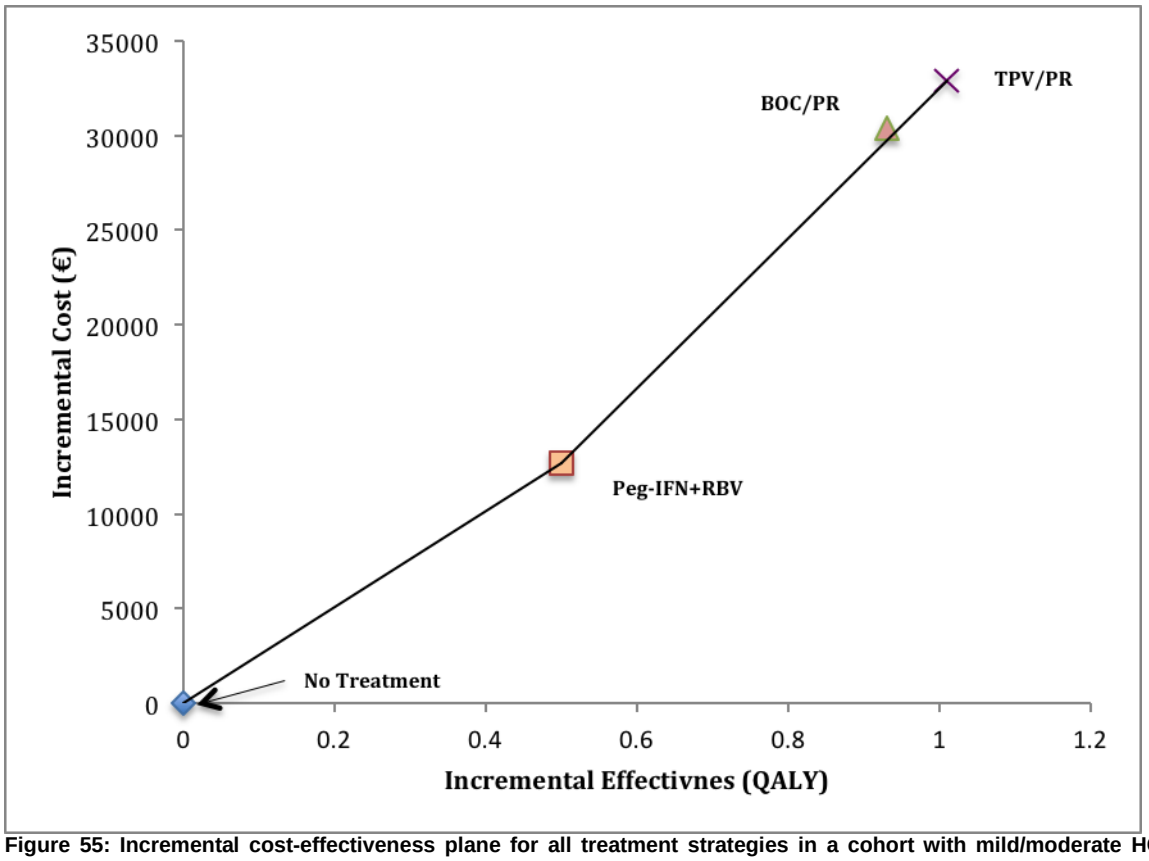


Figure 55: Incremental cost-effectiveness plane for all treatment strategies in a cohort with mild/moderate HCV infection

The line represents the cost-efficiency frontier. Compared with Peg-IFN+RBV, TPV/PR is the most efficient strategy. BOC/PR is subject to extended dominance..

In the NCPE analysis, BOC/PR was the most cost-effective treatment regimen with an ICER of €17,045 when compared to PR and the ICER for TPV/PR versus BOC/PR was above the WTP threshold (€186,230).

8.3.2.3 100% Cirrhotic Population

In the scenario considering only patients with cirrhosis at baseline (100% cirrhotic), the life-time costs are higher than the base case and the QALY gains are lower for all strategies. TPV/PR was the most cost-effective treatment with an ICER of €19,345 compared with PR which was below the WTP threshold (Table 53).

Table 53: Life-time costs, QALY and incremental cost-effectiveness ratio in a cohort with cirrhosis

Strategy	Cost	Effectiveness (QALY)	Incremental Cost	Incremental Effectiveness	ICER
No treatment	€55,265	5.92			
PR	€62,593	6.73	€7,329	0.81	€8,995
TPV/PR	€83,241	7.80	€20,648	1.07	€19,345

BOC/PR was dominated by TPV/PR in this scenario. It was more costly and less effective than TPV/PR (Figure 56).

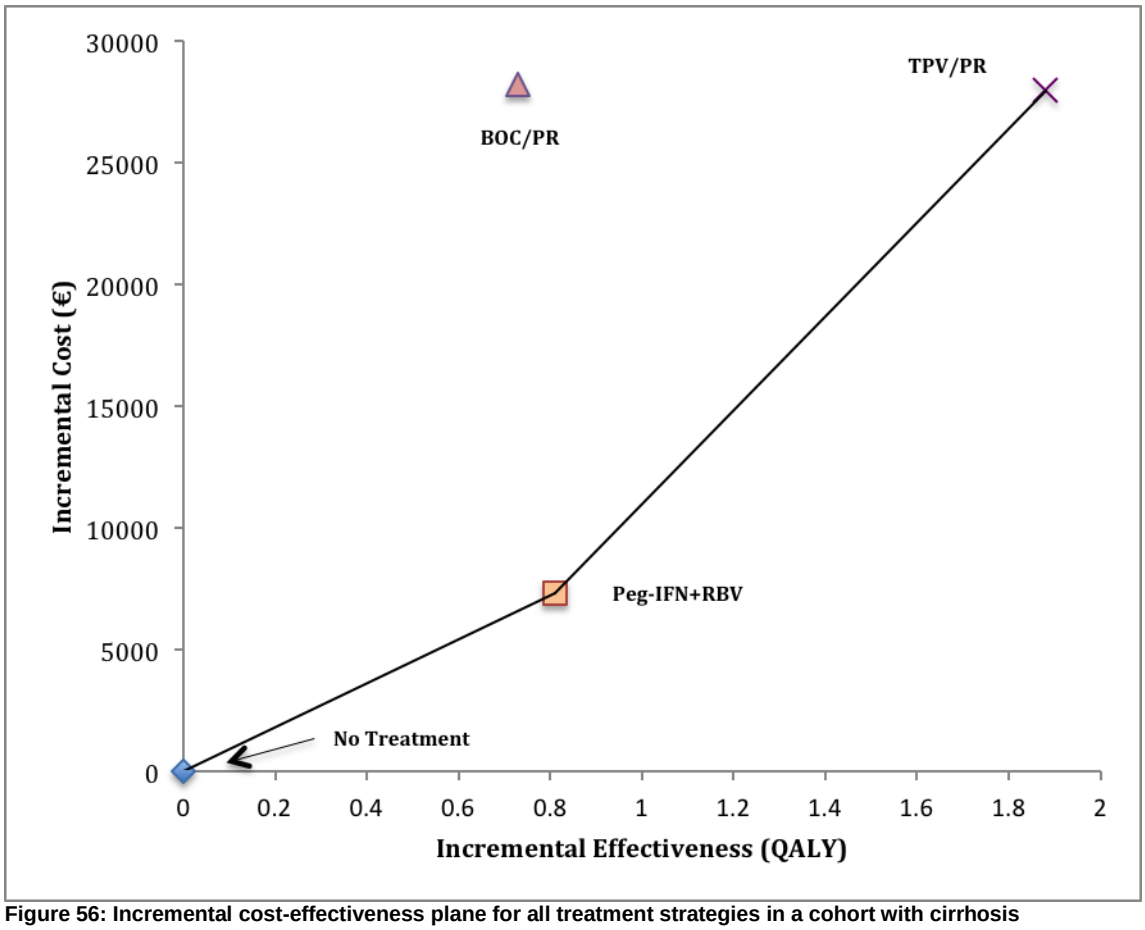


Figure 56: Incremental cost-effectiveness plane for all treatment strategies in a cohort with cirrhosis
The line represents the cost-efficiency frontier. Compared with Peg-IFN+RBV, TPV/PR is the most efficient strategy. BOC/PR is subject to dominated..

Results for this cirrhotic cohort were similar to the results from the analysis by NCPE colleagues, where TPV/PR was the most cost-effective treatment regimen with an ICER of €37,108 versus PR and BOC/PR was dominated.

8.3.3 Discussion

In the analysis completed in 2014 by the NCPE, BOC/PR was reported to be the most cost-effective agent under the conditions of the base case population and in the 100% non-cirrhotic cohort. In that analysis, the data suggested that, from a cost-effectiveness perspective, non-cirrhotic patients should be treated with BOC/PR while cirrhotic patients treated with TPV/PR. However, that model was populated using efficacy data supplied from Phase III clinical trials for BOC/PR and TPV/PR [99, 100, 102, 103, 105]. It made the assumption that the real world effectiveness of treatments would mirror the efficacy of the trials. At the time, it was recognised that this may not have been a true assumption and populating the model with real world data may give a more accurate reflection of cost-effectiveness.

Following the analysis of the real world data from the national HCV treatment registry in previous chapters, the cost-effectiveness model was populated with Irish real world data. In this analysis, TPV/PR was the preferred agent in all three scenarios (base case, 100% non-cirrhotic, 100% cirrhotic). A comparison of the outputs from the two analyses was undertaken. In the real world analysis, under conditions of the baseline population, the proportion of patients without cirrhosis was 65% compared with 80% in the original analysis. The life-time costs in the real world analysis were higher for all treatment regimens and the life-time effectiveness was lower when compared with the initial NCPE analysis using trial efficacy. The ICER for TPV/PR was €28,880 compared with an ICER of €128,082 in the NCPE analysis, which was not considered cost-effective under the Irish WTP threshold of €45,000. In the analysis with real world data, boceprevir was subject to extended dominance in the base case scenario and as a result, the ICER (€28,880) was a comparison of TPV/PR versus PR whereas in the NCPE analysis, BOC/PR was not dominated and therefore, the ICER (€128,082) was a comparison between TPV/PR and BOC/PR. In the scenario with a population of 100% non-cirrhotic patients, the life-time

costs were comparable between the two analyses but the life-time effectiveness was lower in the real world analysis. The ICER for TPV/PR (vs. PR since BOC/PR was dominated) was €39,610 compared with €186,230 (TPV/PR vs. BOC/PR since no treatment was dominated) in the initial analysis which used RCT efficacy inputs. In the scenario with a population of 100% cirrhotic patients, both analyses reported that TPV/PR was the preferred agent. In the real world analysis, the life-time costs and life-time effectiveness (with the exception of TPV/PR) was lower than in the NCPE analysis. The ICER for TPV/PR reported in the real world analysis was €19,345 compared with €37,108 in the original NCPE analysis. Both of these fall under the current WTP threshold. In both analyses, BOC/PR was dominated and therefore, these both represent the ICER of TPV/PR vs. PR.

These data suggest that in the analysis, which incorporated real world data, from a cost-effectiveness perspective, TPV/PR should be the treatment of choice for both cirrhotic and non-cirrhotic patients. The difference in outcomes between the two analyses is largely driven by the difference in SVR rates. In *Chapter 5*, the SVR rate for the TPV/PR cohort was superior to the BOC/PR cohort. Additionally, significant differences were observed in the effectiveness of both TPV/PR and BOC/PR regimens in non-cirrhotic compared with cirrhotic patients.

Increasing healthcare costs have become a major concern for healthcare decision-makers [413]. This study demonstrates the impact that incorporating data from a post-reimbursement observational study can have on the assessment of cost-effectiveness and subsequent recommendations for reimbursement. At present, conclusions regarding reimbursement are drawn from RCTs that have limited value in the decision-making process - assessing the value of a drug or technology requires an understanding of its impact in a real-life setting [414]. Typically, the amount of real world data available for the initial reimbursement

decision is very limited. We demonstrated the impact that incorporating real world data had on the model outputs and therefore we support calls for payers to explore conditional access approval schemes allowing companies to collect the desired evidence through real world use in more targeted populations before a final decision is made [415].

An important strength of this study is the access to individual patient level data. When we examine the inputs applied to the original analysis (Table 47) and compare them with the real world inputs (Table 48), the individual patient level data provides more scope to determine treatment effectiveness probabilities in more specific patient subgroups. Thus, there are more specific real world inputs for incorporation into the economic model.

There are a number of limitations to this analysis. While the analysis using real world inputs reported that TPV/PR was the most cost-effective intervention in all three scenarios presented, this is driven by the superior SVR rate in the TPV/PR cohort reported in *Chapter 5.* While we completed propensity score analyses to address confounding and the non-randomisation of treatment groups, there remains a possibility that there were differences (unmeasured confounders) in the populations treated with BOC/PR versus TPV/PR.

While we have demonstrated the value of real world data, it is necessary to consider the number of patients from which the real world data was generated. In some arms of the model, the numbers were very small (e.g. patients with cirrhosis treated with BOC/PR) and therefore, would be subject to some uncertainty.

Finally, given that the model was run under deterministic conditions, uncertainty around the effectiveness and cost estimates derived from Chapters 5 and 6 results in uncertainty

around the ICER. Further one-way sensitivity analysis and analysis under probabilistic conditions would strengthen the conclusions but this fell outside the scope of this thesis. In probabilistic sensitivity analysis, a random variable from a range of values is chosen for each variable and the model is run over a large number of iterations and allows for a calculation of the overall uncertainty of all the variables in the model. This analysis estimates the probability of an intervention being cost-effective at a given cost-effectiveness threshold. A one-way sensitivity analysis is used to determine the variables that have the greatest impact on the deterministic ICER. Both of these sensitivity analyses are important for managing the uncertainty associated with the deterministic estimate and should be incorporated into future work with this model.

The recent evolution in the treatment of HCV infection has resulted in medicines that offer higher cure rates and fewer adverse events but the cost of the treatment combinations and the large number of infected individuals have raised concerns about their affordability. These treatment regimens are proving to be highly cost-effective but questions are beginning to be asked about how the cost-effectiveness was assessed, whether the clinical pathway was appropriately modelled and all the alternative ways in which treatment can be used were compared [416]. This means that models should include, not only all of the new DAAs therapies, but also the older interferon-based treatments and the possibility of treatment at a later disease stage. Models should also incorporate sequential therapy pathways, whereby a patient who fails therapy is retreated. Traditionally, this has not always been the case. It was assumed that patients were not re-treated if they failed therapy and nor did they have the possibility of delaying treatment until they reached a more severe disease stage [417-426].

In addition to this, there is growing recognition of the importance of capturing the potential downstream benefits of cure for future disease transmission and thus, potentially reducing

the incidence of future infections. Reinfection rates and the impact of treating different patient populations (e.g. PWIDs irrespective of liver-staging vs. non-PWID stage 3 fibrosis) should be routinely incorporated into cost-effective models as the treatment continues to evolve [427, 428]. Furthermore, the impact of interferon-free treatment on liver cancer rates has become an area of significant interest [429-432]. There continues to be substantial uncertainty around whether viral eradication in patients with advanced liver disease is, in fact, beneficial. Disease progression and the development of HCC, despite achieving a SVR, would have a significant impact on the cost-effectiveness analysis and therefore, should also be incorporated into future models so that the ICERs estimated are more reflective of the treatment pathways in clinical practice.

8.4 Conclusion

Observational data has an important role to play in healthcare decision-making. It can add significant value to all health economics and outcomes research-related activities. It can complement traditional clinical development information to guide decision-makers regarding access to and reimbursement of drugs and other healthcare services. It can provide input into drug valuation dossiers and cost-effectiveness models. Given that the volume of observational evidence is usually greater in the post-reimbursement era, observational studies can be valuable for validating previous reimbursement and coverage decisions and providing clear evidence of effectiveness and value.

Demonstrating the value of a drug treatment in clinical practice is becoming more important in a time where the issue of affordability is now a significant problem for payers. Thus, the hierarchy of evidence, which place RCTs and systematic reviews at the peak, is beginning to change. There is now greater recognition of the pitfalls associated with focusing exclusively on efficacy data and more emphasis on the value of incorporating real world data into the decision-making process.

Chapter 9

Chapter 9 Conclusion

9.1 Introduction

This thesis aimed to assess the value of observational data for healthcare decision-making using data from the Irish national HCV treatment registry. In the current era of ever increasing drug costs, healthcare decision-makers must make difficult choices in the

allocation of limited resources in order to maximise health gain. They are increasingly seeking information on real world outcomes on which to base their decisions, and there is a move towards formal post-reimbursement outcomes research at policy level [16, 433]. It is widely recognised that at the conclusion of a RCT, whereby statistical significance of benefit was achieved for a group of ideal patients with no co-morbidities, concurrent medications or behavioural problems, regulatory requirements for licensing are met [434]. However, more often than not, patients in the clinical setting have multiple co-morbidities, are subject to polypharmacy and are not reflective of those 'ideal' patients included in the RCTs. As a result, there is recognised concern about the lack of generalisability of the traditional RCT to the clinical setting [435]. For this reason, decision-makers endeavour to ensure that there is a comprehensive evidence base, including both RCT and population-specific observational data (where available), for the assessment and appraisal of all evidence when making balanced judgements about the management of diseases and for the appropriate allocation of limited resources [11, 13].

Prior research on the cost-effectiveness of HCV medication in Ireland focused on determining the relative efficacy of early DAA regimens for GT1-infected patients and developing an economic model to assess the cost-effectiveness of these agents independent of manufacturers' economic models [81, 82, 253, 436]. However, Irish real world data associated with the clinical effectiveness and direct treatments costs for novel DAA-agents were lacking, and the impact of such data on cost-effectiveness was, heretofore, not explored. Furthermore, there has been little research into the value of observational data using practical examples such as treatment registries. The HCV treatment registry was the first national multidisciplinary treatment registry established in Ireland and therefore, provided an opportunity to assess its value and determine whether there is potential for applying the principles of observational research to other therapeutic areas.

The objectives of this thesis were to establish the effectiveness data from the registry for DAA treatment regimens licensed for use in Ireland. The robustness of our observational data was explored using a method commonly applied to address confounding. The rates of efficacy reported in RCTs and effectiveness in international real world studies for patients with HCV GT1-infection were systematically identified and the SVR rates were compared between the two data sources and with our data. We aimed to establish the direct costs of treating HCV infection and the direct HCV-related healthcare costs during treatment and following the achievement of a SVR from the perspective of the Irish payer. Additionally, we set out to determine the attitudes and perceptions of Irish healthcare stakeholders to the national HCV registry and to examine the practical applications for this real world data.

9.2 Main Findings

The systematic literature review described in *Chapter 4* provides clear evidence that the populations included in clinical trials tend not to reflect the population treated in the clinical setting and as a result, the efficacy rates often differ from the effectiveness rates reported in the real world. Clinical trials commonly exclude difficult-to-treat patients, those with the most severe presentation of a disease (e.g. decompensated cirrhosis) and/or those with co-morbid conditions (e.g. HIV-co-infection or renal insufficiency). While appropriate eligibility criteria are essential for the internal validity of the RCTs, it often results in the selection of an 'ideal' patient population most likely to demonstrate the efficacy and safety outcomes required to ensure regulatory approval. Historically, Phase III RCT evidence has been considered the gold standard in the hierarchy of evidence for evaluating the efficacy and safety of interventions. The BTD aims to fast-track the approval of marketing authorisations for promising drugs, potentially relying exclusively on well-controlled, non-comparative studies as appropriate evidence of efficacy for regulators. Thus, not only does the RCT population poorly reflect the clinical setting but we also consider whether the BTD compromises the scientific strength of the RCT evidence at the top of the

evidence hierarchy. Without the requirement for randomisation, blinding and concealment, the design of these non-randomised and/or non-comparative studies for BTD designated treatments do not differ significantly from the design of observational studies. Licensing of treatments for HCV infection in recent years is a testament to this phenomenon whereby many agents and treatment regimens were licensed based on non-comparative, single arm studies driven by the desire to bring treatments to the market as quickly as possible. This has also occurred in a number of other therapeutic areas. Therefore, as observational studies may be more reflective of the real world populations and the design of the study may not differ significantly from that of a RCT, it is now more important than ever that decision-makers consider the evidence from observational studies accrued prospectively in the post-HTA era, in addition to the RCT evidence, and the quality of this evidence, to inform or revise policies and decisions about coverage and reimbursement.

Well-designed observational studies provide robust information important for health economics and outcomes research. The treatment effectiveness findings in *Chapter 5* and the treatment costs reported in *Chapter 6* demonstrates their value in providing real world data from the clinical setting while also providing outcomes in subpopulations rarely included in RCTs (e.g. in patients with decompensated cirrhosis). For the IFN-based regimens, our effectiveness rates were comparable to those reported in the trials assessing the efficacy of these treatment regimens, but feedback from the treatment sites indicated that patients treated with these complex regimens required intensive monitoring, as evidenced by the costs determined in this work. These on-treatment management costs (costs excluding HCV drug acquisition costs) were primarily driven by the high rates of AEs associated with these regimens and provided intense impetus for the availability of the IFN-free regimens. The effectiveness rates for patients treated with the IFN-free regimens were lower than those reported in the RCTs, attributable to the broader patient populations included in our study. The introduction of prioritisation criteria in Ireland (supported by the EAP) allowed access to treatment with IFN-free regimens for patients

with advanced liver disease, considered to be of greatest clinical need. Effectiveness rates in this difficult-to-treat cohort were significantly lower than the reported efficacy rates from trial data but the trials had largely excluded this subpopulation. Findings from the studies reported in this thesis had practical and important implications for the care and management of patients in Ireland and demonstrated the value of prospective accrual of real world outcomes. Analysis of the outcomes in patients with advanced liver disease treated with IFN-free regimens in early 2015 reported a high mortality rate, which was disseminated from the registry to the clinical members of ICORN [361]. As a direct result of this analysis, patients with advanced liver disease (CTP C) were no longer considered suitable for treatment and were preferentially referred for transplantation assessment. Evidence of the enhanced effectiveness of IFN-free treatments in patients with less severe liver disease i.e. increasing SVR rates in a compensated cirrhotic cohort, as reported in this thesis show that as the patient populations begin to emulate the populations included in the original trials, effectiveness rates become increasingly comparable to reported efficacy rates.

The micro-costing study in *Chapter 6* established that the direct costs associated with HCV treatment in Ireland are substantial (€38,286 and €55,734 for IFN-based and IFN-free regimens, respectively). However, these are mainly driven by the high acquisition cost of the HCV medication. When the drug acquisition costs are excluded, the cost of the management of AEs for IFN-based regimens was the most costly component of the treatment management costs. This is an important consideration for the healthcare payer. Currently access to IFN-free regimens are limited to patients with moderate to severe liver disease i.e. MF2 or greater, or ISHAK stage 3 or greater, while IFN-based regimens can continue to be accessed by patients with MF0-1 or ISHAK stage 1-2 [437]. The additional costs of management of AEs for these regimens merit review, as costs of treatment may, in effect, be comparable to treatment with IFN-free regimens. Additionally, the high rate of premature discontinuations and the substantial mean annual costs reported in the post-

discontinuation period provide further evidence against the use of IFN-free regimens, irrespective of the severity of disease. The study determined that for IFN-free regimens in patients treated in the EAP, inpatient admissions were the largest contributor to the on-treatment management costs - a direct result of the advanced nature of the disease in this cohort. As the IFN-free regimens have become available to patients with milder liver disease, the SVR rates have increased, as evident in our assessment of patients with compensated cirrhosis. This will be accompanied by a reduction in the cost of treatment-related monitoring and AEs, the inpatient admissions and consequently, the mean cost of treatment and the mean cost per SVR. Additionally, while we demonstrated that the costs in the post-SVR period for our population of patients with advanced liver disease was high, in the long-term we anticipate that the HCV-related post-SVR healthcare costs to be lower than the HCV-related healthcare costs of untreated HCV-infected patients. It is also anticipated that patients with mild disease may be discharged entirely from clinical care in the hospital setting, thus representing significant savings to the payer. This provides justification for the use of these high cost DAA regimens and demonstrates long-term HCV-related healthcare cost reductions in the HCV-infected cohort.

Chapter 7 reported the findings from the survey to determine the perceptions, knowledge and attitudes among key stakeholders to the registry. Establishment of the registry was associated with considerable difficulties including operational issues and the need to overcome barriers among under-resourced staff in the treatment sites. Undertaking the survey was thought to be important, as the registry has become pivotal to the newly established National Treatment Programme. The opinions of key stakeholders involved in the day-to-day aspects of it were important in determining practical issues of potential difficulty and to ensure that as the registry transitions to a disease registry, that it does so with ease. Findings from the survey indicate high levels of satisfaction with the registry, but a number of important issues were identified that have the potential to enhance the value and practical use of the registry. The efficiency of the operational aspects,

particularly for nursing staff, was a key concern and the transition to an electronic platform accessible to all stakeholders was suggested. Improving communication of outcomes was another key finding. Stakeholders felt the current standards of reporting and disseminating research outcomes were inadequate and the promotion of better channels of communication and standards were required.

In *Chapter 8,* the findings from the systematic literature review in *Chapter 4* and the effectiveness rates reported in *Chapter 5* were incorporated into a NMA, and the effectiveness rates from *Chapter 5* and costs reported in *Chapter 6* were incorporated into an economic model with the aim of examining the practical applications of these real world data and their value in the healthcare decision-making process. Our findings demonstrate that the inclusion of observational data in the NMA did not impact on treatment rankings. Similarly, no pattern was observed in the changes to the standard deviation or 95% credible intervals that would have indicated that the inclusion of observational data reduced uncertainty. While including additional data from observational studies will increase the evidence available in NMAs, at present there is substantial uncertainty surrounding the methodology used to develop the model and connect the network and therefore, we cannot make any significant conclusions about the value of adding this data. We recommend that further work is completed to develop reliable strategies for incorporating non-comparative studies into the NMA and for appropriately down-weighting evidence from studies of differing design before we can make any firm conclusion about the value of including observational data in a NMA.

Utilising real world effectiveness rates and real world cost data into the economic model, developed *de nova* by the NCPE, altered the findings of the model when compared with the original analysis. While the initial analysis reported that BOC/PR was the most cost-effective agent under conditions of the base case population, the analysis incorporating the real world data reported that TPV/PR was the most cost-effective agent in the base

case scenario. This finding would support the introduction of conditional reimbursement by the payer whereby the treatment is reimbursed conditional on the collection of further observational evidence, at which point the combination of RCT and the real world data can allow for a final reimbursement decision to be made.

9.3 Limitations

Limitations of the studies performed within this thesis are detailed in *Chapter 3* and in the individual study chapters. The non-randomised nature of observational research remains an important concern. In addition to the known biases, data is potentially subject to hidden biases as a result of unmeasured confounders that are difficult to address. Despite taking the necessary steps to reduce the potential for bias in this research, we must recognise that bias in observational studies cannot be eliminated and should be accounted for when interpreting outcomes. While taking measures to adjust for confounding, after the application of propensity scoring in our data, there was no difference in treatment effect observed. While statistical significance was demonstrated, the numbers included in the analysis were too few to allow for convincing conclusions to be drawn from the data. Despite this, propensity score adjustment is a tool that can be applied to future analyses of the outcomes from the registry as the size of the national treatment registry grows with the availability of additional treatment regimens and as the capacity to treat increases.

The quality of the data from the registry must be considered. While strict quality control procedures were adhered to at all stages of the data collection and inputting process, it is possible that there were minor inaccuracies in the data. Unlike many other registries world wide, the Irish HCV treatment registry is not presently linked to any electronic databases and thus, all steps in the process are completed manually. This process commences with the medical team recording the clinical notes into patient charts and EPR, continues to the data collectors extracting the data from the charts and EPR and ends with the process of

inputting these data into the registry. Therefore, there are many steps along the process with potential for errors to occur. However, the strict quality control procedures, as outlined in *Chapter 3*, and the ability to case-find and alter data point anomalies has overcome many of these issues.

Another important limitation is the relatively small patient numbers included in our studies, to date. The population in Ireland, in general, is small when compared with the population in other countries who have published their treatment outcomes in HCV-infected patients. The number of patients infected with HCV is numerically smaller and consequently, the capacity to treat is lower. As a result, the studies in this thesis report outcomes in cohorts of patients that are significantly smaller than the cohorts published from other countries [157, 290, 330, 338, 349]. As we examined outcomes in subpopulations, such as those with decompensated cirrhosis or with specific genotypes, the numbers in the cohorts became even smaller. This may limit the generalisability of the results and in some cases, limit meaningful analysis. Despite this, our results were comparable to real world study findings in other jurisdictions.

In the systematic literature review, we recognise the potential for publication bias. While all resources and search strategies were used to ensure all relevant studies were included, it is possible that trial sponsors failed to report the results of unfavourable trials and thus, the potential for publication bias must be considered. Additionally, in that study, the pooling of data from studies with heterogeneous design requires awareness of the potential to introduce bias. Whilst pooling is the simplest and most intuitive way of summarising the information from several clinical trials, this approach does not consider the validity of the comparisons, assumes all trial designs are the same and therefore, is often subject to bias. If not recognised, these could have had implications on further work

completed in this thesis, where these data from the systematic review were incorporated into the NMA.

9.4 Impact on Health Policy

In 2011, the first generation protease inhibitors, TPV and BOC, were the first DAAs to be licensed in Ireland for use in HCV GT1-infected individuals in combination with PR, and following the HTA process were reimbursed for treatment [88]. The availability of these therapies represented an opportunity to maximise stewardship of the therapeutic management of HCV infection in Ireland through the establishment of a treatment registry, ensuring optimal clinical and economic outcomes from the use of new agents in the clinical setting. As a result, ICORN and the national HCV treatment registry was established and reimbursement of these regimens was contingent on the collecting and reporting of real world effectiveness and cost outcomes.

At the end of 2014, the early access to potent IFN-free regimens in Ireland, granted by the HSE prior to the evaluation of cost-effectiveness, was significant. Although recognised as clinically effective treatments with significantly improved treatment outcomes, the cost of these drugs place a significant burden on healthcare systems worldwide and have the potential to displace significant amounts of healthcare within and outside the area of HCV [438]. Ensuring accessibility and appropriate allocation of these regimens in Ireland was the next step forward. In an ideal world, the most tolerable and efficacious treatments would be immediately available to every patient. Yet, in the face of finite health budgets, there is no HCV single treatment strategy that is optimal with regard to all public-health outcomes, and each involves a trade-off. For instance, while prioritising patients with advanced liver disease will have maximum impact on liver-related complications, it is suboptimal in curtailing the transmission rate which would require targeting PWIDs [439]. A number of strategies were implemented by different countries to address the issue of affordability;

the universal approach, while potentially suboptimal, was aimed at prioritisation based on clinical need.

In Ireland, an Expert Advisory Group was established by the Department of Health tasked with advising on the best approach for allocating treatment. The group recommended that, in order to optimise patient outcomes, a National Hepatitis C Treatment Programme be established and clinical prioritisation criteria be defined which would facilitate the identification of patients at greatest clinical risk. The success of the national HCV treatment registry in the reporting of the patient demographics, clinical and economic outcomes for the DAA triple therapy regimens, presented in *Chapters 5 and 6,* was fundamental to this recommendation. The power and value of these data generated from the treatment registry was recognised and the group advised on the evolution of the treatment registry into a national HCV disease registry. The aim of the disease registry would be to assist with future treatment planning and strategies.

Based on international evidence and advice from clinical experts [76, 158], the advisory group proposed that, in Ireland, treatment allocation would be phased and patients would be prioritised for each phase based on their clinical need under a multi-annual treatment plan. Consequently, prior to the commencement of each phase of the treatment strategy, patient data from each of the seven hospital sites, which were deemed to match the required prioritisation criteria, was submitted to the newly expanded disease registry. The data for each patient was reviewed and those meeting criteria were approved to commence treatment.

Now the registry not only contains data on patients who have commenced (or completed) treatment with DAA agents (IFN-based and IFN-free) but it also includes data on patients awaiting approval for treatment. While continuing to monitor the clinical effectiveness and economic outcomes of the new drug regimens, the registry now provides a very clear

picture of the profile of patients receiving treatment and the risk profile and clinical status of those who are engaged with care and waiting treatment. From an operational point of view, and cognisant of the feedback from the survey, the registry will transition to an electronic user-friendly format by Quarter 4 2016. This will reduce the paper-burden of the current system and in addition, will innovatively pull data directly from the Patient Administration Systems in the individual treatment sites, an example of linking data similar to the TrolleyGAR system in operation by the HSE [440, 441]. This will be a fundamental improvement to the registry given that the capacity to treat is anticipated to increase when the IFN-free regimens become available to patients without cirrhosis, as the requirement for intensive on-treatment monitoring lessens.

The real world clinical and costs data will continue to inform treatment decisions both for individuals but also for subgroups within the HCV population in Ireland. The inclusion of patients engaged with care and awaiting treatment allows for more informed decision-making on the most appropriate clinical pathways and drug treatments for patients. Furthermore, the data are being used to inform drug reimbursement decisions and are also proving useful in strategic negotiations with the pharmaceutical suppliers, in terms of reducing the acquisition costs of the treatment regimens.

9.5 Implications for the future

Establishment of Irish values for the effectiveness and HCV-related costs, in particular the on-treatment monitoring costs, for DAA-regimens will facilitate more robust HTAs of future HCV agents in Ireland. While these data apply to currently reimbursed regimens, this research provides a clear view of the expected differences between the efficacy and effectiveness rates of HCV regimens. With the completion of this research, there is now Irish data available on the costs of untreated HCV, on-treatment HCV-related costs, the mean annual cost post-discontinuation and the mean annual post-SVR costs. These data

will be highly valuable to healthcare policy-makers as they continue to manage the budget impact of these high cost drugs.

The treatment registry provided an accurate national account of the number of HCV-infected patients who have received treatment with DAA regimens and their demographics. Additionally, with the evolution to the disease registry and by combining these data with data from previous studies, we can estimate the total number of patients who have received treatment and the total number of patients awaiting treatment. The registry also facilitates the recording of the treatment outcomes in one central database and the identification of those who have required re-treatment. These data allow for a national overview of the capacity to treat with current and future HCV regimens and allow for the future planning of resource allocation and utilisation.

The outcomes from the quantitative survey were important to ensure the future success of the registry. The survey identified the importance of reducing the administrative tasks and workload of the nursing staff, in particular. The introduction of an electronic platform for patient registration was identified as a solution, and is currently being addressed. The introduction of the IHIs, a unique personal number across all health and social services, is a key part of the government's e-health strategy. It will be a further resource to facilitate the linkage and integration of data across care settings. Harnessed correctly, this will be important for the continued success of the registry and increase the value of the findings. Additionally, in recognition of the need for communication regarding the registry outcomes, a formal annual report will now be available through the National Treatment Programme.

In *Chapter 8* we identified the need for more appropriate methods of forming 'connected networks' when including non-comparative studies in NMAs. There was significant

uncertainty surrounding the results in this study, driven mainly by the development of a novel method for connecting the network by Leahy *et al* [407]. However, without using this methodology to connect the network, an estimation of the relative treatment effect for all licensed regimens for GT1 HCV infection would not have been possible. As more and more treatments become available for HCV in the future, it is important to have greater confidence in the estimates of relative treatment effect for use in economic evaluations. We recommend that further work be completed to develop reliable strategies for incorporating non-comparative studies in the NMA.

With the success of the HCV treatment registry in Ireland, healthcare policy-makers should look to implement similar studies in other therapeutic areas. The research conducted as part of this thesis has demonstrated the value of these data in one particular therapeutic area, and provides evidence of the value and need for application to other therapeutic areas where drug acquisition costs are considerable or where cost-effectiveness has not been established. A recent study provided real world survival outcomes for patients with advanced malignant melanoma treated with ipilimumab, a high cost anti-cancer drug, in Ireland [442], and noted the disparity between efficacy rates and effectiveness rates in real world practice. Findings from this study have prompted decision-makers to review the potential for linking data from the National Cancer Registry of Ireland with outcome data following treatment. Similarly, the high cost of the PSK-9 inhibitor evolocumab for hypercholesterolaemia has prompted the need for prospective accrual of data, not only to ensure that the correct patient populations are selected for treatment, but also to determine the outcomes post-treatment [400]. Given there is an increasing need to control healthcare expenditure and demonstrate increased value for money in the Irish healthcare system, there is considerable potential for prospective, longitudinal observational outcomes research studies, registries and other databases to provide valuable data in many other therapeutic areas.

From a broader context, not only have we developed a framework for an observational outcomes research portfolio facilitated through treatment and disease registries that can be applied to other high-cost therapeutic areas but we have also demonstrated the impact of prospective, longitudinal observational evidence on health-policy. However, there continues to be significant variation in the standard of observational studies undertaken worldwide which is contributing to some resistance in the acceptance of observational studies for use in healthcare decisions. Patient care decisions demand high quality research. To assist those decisions, numerous observational studies are being performed. In order for payers and decision-makers to fully embrace and accept observational evidence, there needs to be greater confidence in the quality of the study designs and outcomes reported. This has raised questions whether the development of guidelines and the implementation of standards for the conduct of observational studies would give rise to greater recognition in the decision-making process without compromising the real world value, and generalisability, of the evidence.

At present, the STROBE statements and GRACE principles are the closest we have to any guidelines relating to observational studies. However, they do not provide guidance for the conduct and design, but provide a checklist for the reporting of and assessing observational studies in terms of quality for usefulness of decision making, respectively [273, 443]. Following on from our research and from analysing outcomes from the observational studies identified in our systematic literature review, we advocate for the development of principles for the design and conduct of these studies in order to maximise their value. The defining strength of observational studies is the fact that they monitor the outcomes of patients in their natural environment. It is essential that any guidelines do not compromise this strength. However, we believe that there should be guidance and standards around the study setting, the sample size and power and the

outcomes to be assessed. While each disease area/condition needs to be considered separately, there should be guidance around the 'natural environment', ensuring that it is suitable for assessing the outcome of interest and reflective of the treatment pathway for the disease/condition under investigation. Having observed significant fluctuations in the number of subjects included in the observational studies identified in *Chapter 4*, we believe that the sample size and power of the observational study should be performed and considered in order to assure confidence in the study results and conclusions while accepting that there are circumstances where it is impossible to include a sufficient sample size into an observational study such as in our study, where the sample was limited by the capacity to treating in each study centre. Finally, standardised outcomes, again specific to each condition/disease, would enable comparability between studies and would facilitate the pooling of data from multiple studies, particularly in instances where the studies had insufficient power to detect statistically significant outcomes. OMERACT is an example where an internationally, informally organised network was formed with the aim of improving outcome measures in rheumatology [444]. The network were committed to determining relevant health outcome domains and endorsing valid, responsive, feasible health outcome measures in patients with musculoskeletal conditions and is an example of an initiative that could be incorporated into other disease areas, such as hepatitis C.

In HCV, an initiative similar to OMERACT could facilitate a consensus on the outcomes required to be measured in observational studies. By establishing consensus on outcome measures, such as SVR12, the same outcome will be gathered across all studies types, from RCTs to observational studies, increasing the body of evidence available for use in evidence synthesis and preventing the exclusion of studies deemed 'invaluable' as a result of their use of an alternative outcome measure. Additionally, an international network could identify treatment regimens where real-world outcome data is lacking or where additional head-to-head data would be beneficial and agree to undertake collaborative, observational studies including these identified regimens. Such studies

would be also be highly valuable in evidence synthesis where difficulties continue to arise in network meta-analyses and the formation of connected networks as discussed in *Chapter 8*. Finally, while SVR is the outcome measure most commonly reported, such a network could commit to designing longer-term studies, focusing on outcome measures such as the development of liver cancer and liver disease progression.

The use of real world data is critical to transforming healthcare and policies need to address this issue. There is now a vast volume of observational studies undertaken, it is important that they are conducted in such as way as to ensure that the outcomes are valid and that they receive the recognition that they deserve. The development of standardised guidelines would enable decision-makers to have greater confidence in the outcomes from observational studies.

Another method of improving the acceptability of observational studies would be a requirement to register observational studies, much like the current process for registering clinical trials. Clinical trial registers are established tools for improving access to information on trials and for addressing publication bias and reporting bias [445]. As with clinical trials, incomplete reporting of observational studies has been documented. It has also been suggested that observational studies are at increased risk for publication bias or other types of bias, including misrepresentation of pre-specified analyses. Such biases are concerning given that they can undermine the validity of observational studies and their importance and value to the evidence base. Registering of these studies would ensure that there was record of observational studies commenced and ideally, reducing those studies where no outcomes, or outcomes that differed from those that were pre-specified, were reported. This register would provide decision-makers and researchers with a more comprehensive view of the growing evidence base.

9.6 Conclusions

This thesis demonstrates the value of observational data in healthcare decision-making. While the use of data from observational studies exclusively for regulatory approval and licensing is not advocated, healthcare decision-makers should incorporate these data with all other available evidence when making decisions that will inform health policy.

A framework for a prospective, longitudinal, observational outcomes research portfolio facilitated through treatment and disease registries has now been developed. Policy-makers in other therapeutic areas can adopt this framework as they strive to more clearly demonstrate the effectiveness and value of interventions using combinations of evidence that is compelling to decision-makers.

Finally, given the volume and variation in the quality of observational studies undertaken, we advocate the need for guidelines for the design and conduct of these studies. Without compromising the ‘natural environment’, it is important that there is comparability between studies conducted in the same disease area and that decision-makers have confidence in the quality of the research undertaken and the outcomes reported.

Appendices

Appendices

Appendix 1: Systematic Literature Review

Search Strategy

Search Terms for PubMed

(((((((telaprevir AND Randomized Controlled Trial[ptyp])) OR (boceprevir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (simeprevir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (sofosbuvir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (ledipasvir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (daclatasvir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (paritaprevir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh])) OR (ombitasvir AND Randomized Controlled Trial[ptyp] AND Humans[Mesh]) AND (Randomized Controlled Trial[ptyp] AND Humans[Mesh])

OR

((((((((((((ombitasvir) AND real world studies)) OR ((paritaprevir) AND real world studies)) OR ((paritaprevir) AND real world studies)) OR ((ledipasvir) AND real world studies)) OR ((daclatasvir) AND real world studies)) OR ((sofosbuvir) AND real world studies)) OR ((simeprevir) AND real world studies)) OR ((boceprevir) AND real world studies)) OR ((telaprevir) AND real world studies))) OR ((((((((((ombitasvir AND (Observational Study[ptyp]))) OR (paritaprevir AND (Observational Study[ptyp]))) OR (daclatasvir AND (Observational Study[ptyp]))) OR (ledipasvir AND (Observational Study[ptyp]))) OR (sofosbuvir AND (Observational Study[ptyp]))) OR (simeprevir AND (Observational Study[ptyp]))) OR (boceprevir AND Observational Study[ptyp])) OR (telaprevir AND Observational Study[ptyp])) AND Observational Study[ptyp])) OR (((((((telaprevir) AND real world)) OR ((boceprevir) AND real world)) OR ((sofosbuvir) AND real world)) OR ((simeprevir) AND real world)) OR ((ledipasvir) AND real world)) OR ((daclatasvir) AND real world)))

Translations

Humans[Mesh]	"humans"[MeSH Terms]
ombitasvir	"ABT-267"[Supplementary Concept] OR "ABT-267"[All Fields] OR "ombitasvir"[All Fields]
studies	"Studies"[Journal] OR "studies"[All Fields] OR "Stud Inst Divi Thomae"[Journal] OR "studies"[All Fields] OR "Brigham Young Univ Stud"[Journal] OR "studies"[All Fields]
world	"WORLD"[Journal] OR "world"[All Fields]
paritaprevir	"ABT-450"[Supplementary Concept] OR "ABT-450"[All Fields] OR "paritaprevir"[All Fields]
ledipasvir	"ledipasvir"[Supplementary Concept] OR "ledipasvir"[All Fields]
daclatasvir	"BMS-790052"[Supplementary Concept] OR "BMS-790052"[All Fields] OR "daclatasvir"[All Fields]
sofosbuvir	"sofosbuvir"[MeSH Terms] OR "sofosbuvir"[All Fields]
simeprevir	"simeprevir"[MeSH Terms] OR "simeprevir"[All Fields]
boceprevir	"N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-((((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide"[Supplementary Concept] OR "N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-((((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide"[All Fields] OR "boceprevir"[All Fields]
telaprevir	"telaprevir"[Supplementary Concept] OR "telaprevir"[All Fields]

Search Terms for EMBASE

1. 'telaprevir'/exp OR telaprevir AND [randomized controlled trial]/lim AND [humans]/lim

2. 'boceprevir'/exp OR boceprevir AND [randomized controlled trial]/lim AND [humans]/lim

3. #**1** OR #**2**

4. ‘telaprevir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

5. ‘boceprevir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

6. #**4** OR #**5**

7. #**3** OR #**6**

8. simeprevir AND [randomized controlled trial]/lim AND [humans]/lim

9. ‘simeprevir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

10. #**8** OR #**9**

11. sofosbuvir AND [randomized controlled trial]/lim AND [humans]/lim

12. ‘sofosbuvir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

13. #**11** OR #**12**

14. daclatasvir AND [randomized controlled trial]/lim AND [humans]/lim

15. ‘daclatasvir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

16. #**14** OR #**15**

17. ledipasvir AND [randomized controlled trial]/lim AND [humans]/lim

18. ‘ledipasvir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

19. #**17** OR #**18**

20. paritaprevir AND [randomized controlled trial]/lim AND [humans]/lim

21. ombitasvir AND [randomized controlled trial]/lim AND [humans]/lim

22. ‘ombitasvir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

23. ‘paritaprevir’/exp AND [randomized controlled trial]/lim AND [humans]/lim

24. #**20** OR #**21**

25. #**22** OR #**23**

26. #**24** OR #**25**

27. ‘telaprevir’/exp OR telaprevir

28. ‘observational study’

29. ‘real world’

30. #**27** AND (#**28** OR #**29**)

31. ‘boceprevir’/exp OR boceprevir

32. ‘simeprevir’/exp OR simeprevir

33. ‘sofosbuvir’/exp OR sofosbuvir

34. ‘ledipasvir’/exp OR ledipasvir

35. ‘daclatasvir’exp OR daclatasvir

36. ‘paritaprevir’/exp OR paritaprevir

37. ‘ombitasvir’/exp OR ombitasvir

38. #**29** AND #**31**

39. #**29** AND #**32**

40. #**29** AND #**33**

41. #**29** AND #**34**

42. #**29** 84 AND #**35** 90

43. #**29** AND #**36**

44. #**29** AND #**37**

#**7** OR #**10** OR #**13** or #**16** OR #**19** OR #**26** OR #**30** OR #**38** OR #**39** OR #**40** OR #**41** OR #**42** OR #**43** OR #**4**

Table A 1: Baseline demographics of all patients included in clinical trials identified in the systematic review

Study	Year	Drug Treatment	Comparator	N		Male (%)		G1a (%)		Treatment Experienced (%)		Presence of cirrhosis (%)		SVR Rate (%)	
				Drug Treatment	Comparator	Drug Treatment	Comparator	Drug Treatment	Comparator	Drug Treatment	Comparator	Drug Treatment	Comparator	Drug Treatment	Comparator
Jacobson *et al*	2011	TPV/PR	PR	363	361	59	58.4	58.7	57.6	0	0	5.8	5.8	74.7	43.8
McHutchison *et al*	2009	TPV/PR	PR	158	75	64.6	57.3	65.2	66.7	0	0	0	0	63.9	41.3
Hezode *et al*	2009	TPV/PR	PR	81	82	66.7	54.9	38.3	42.7	0	0	0	0	69.1	46.3
McHutchison *et al*	2010	TPV/PR	PR	115	114	67.8	66.7	60	62.3	100	100	16.5	11.4	51.3	14
Zeuzem *et al*	2011	TPV/PR	PR	530	132	70.2	67	45.1	44.7	100	100	26.2	22.7	65.3	16.7
Sherman *et al*	2011	TPV/PR		440	-	61.6	-	71.8	-	0	-	9.5	-	83	-
Kumada *et al*	2012	TPV/PR	PR	126	63	52.4	52.4	1.6	0	0	0	0	0	73	49.2
Kwo *et al*	2010	BOC/PR	PR	206	104	52.9	67.3	54.9	51	0	0	6.3	7.7	65.5	37.5
Poordad *et al*	2011	BOC/PR	PR	734	363	61.3	56.7	64.2	62.5	0	0	5.4	3.6	64.7	37.7
Bacon *et al*	2013	BOC/PR	PR	323	80	65	72.5	58.8	57.5	100	100	12.1	12.5	62.5	21.3
Flamm *et al*	2013	BOC/PR	PR	134	67	72.4	64.2	56	56.7	100	100	17.9	13.4	64.2	20.9
Fried *et al*	2014	SMV/PR	PR	156	77	55.8	50.6	47.4	37.7	0	0	0	0	81.4	64.9
Zeuzem *et al*	2014b	SMV/PR	PR	199	66	68.3	63.6	41.2	40.9	100	100	12.1	12.5	62.5	21.3
Forns *et al*	2014	SMV/PR	PR	260	133	68.6	59.4	42.3	40.6	100	100	15.8	14.3	72.9	36.1
Jacobson *et al*	2014	SMV/PR	PR	264	130	56.1	56.9	55.7	56.9	0	0	11.7	13.1	79.5	50
Manns *et al*	2014	SMV/PR	PR	257	134	54.5	57.5	40.9	40.3	0	0	6.6	11.2	50	79.5
Reddy *et al*	2015	SMV/PR	TPV/PR	379	384	64.1	58.1	43	42.2	100	100	23.2	19.5	53.6	54.7
Kowdley *et al*	2013	SOF/PR		161	-	60.9	-	77.6	-	0	-	0	-	88.8	-
Lawitz *et al*	2013b	SOF/PR		292	-	64	-	77.1	-	0	-	100	-	89.4	-

Lawitz *et al*	2013a	SOF/PR	PR	47	26	44.7	73.1	74.5	76.9	0	0	0	0	89.4	57.7
Pol *et al*	2012	DCV/PR	PR	12	12	58.3	66.7	75	58.3	0	0	0	0	83.3	25
Osinusi *et al*	2013	SOF+RBV		25	-	76	-	80	-	0	-	4	-	68	-
Chulanov *et al*	2014	SOF+RBV		34	-	N/A	N/A	N/A	N/A	0	-	82.4	-	76.5	-
Lalezari *et al*	2013	SOF+RBV		38	-	N/A	N/A	78.9	-	0	-	N/A	-	50	-
Lawitz *et al*	2014a	SOF/SMV±RBV		167	-	64.1	-	77.2	-	76	-	24.6	-	92.2	-
Kwo *et al*	2015	SOF/SMV±RBV		310	-	N/A	N/A	N/A	N/A	29.7	-	0	-	89.7	-
Lawtiz *et al*	2015	SOF/SMV±RBV		103	-	N/A	N/A	N/A	N/A	51.5	-	100	-	83.5	-
Kowdley *et al*	2014b	3D±RBV		201	-	54.2	-	65.7	-	20.9	-	0	-	92.5	-
Feld *et al*	2014	3D±RBV		473	-	57.3	-	68.1	-	0	-	0	-	96.2	-
Zeuzem *et al*	2014a	3D±RBV		297	-	56.2	-	58.2	-	100	-	0	-	96.3	-
Poordad *et al*	2014	3D±RBV		380	-	70.3	-	68.7	-	57.9	-	100	-	93.7	-
Ferenci *et al*	2014	3D±RBV		724	-	54	-	42.1	-	0	-	0	-	96.4	-
Dore *et al*	2015	3D±RBV	TPV/PR	337	122	53.7	50.8	26.1	33.6	30	38.5	0	0	98.2	74.6
Andreone *et al*	2014	3D±RBV		186	-	54.8	-	0	-	100	-	0	-	98.4	-
Sulkowski *et al*	2014	DCV/SOF±RBV		152	-	53.9	-	79.6	-	27	-	0	-	98	-
Bourliere *et al*	2015	SOF/LDV±RBV		155	-	73.5	-	63.2	-	100	-	100	-	96.1	-
Lawitz *et al*	2014b	SOF/LDV±RBV		100	-		-	87	-	40	-	22	-	97	-
Afdhal *et al*	2014b	SOF/LDV±RBV		440	-	65.2	-	76.6	-	100	-	20	-	97	-
Kowdley *et al*	2014a	SOF/LDV±RBV		647	-	58	-	79.6	-	0	-	0	-	96.4	-
Afdhal *et al*	2014a	SOF/LDV±RBV		865	-	59.3	-	67.2	-	0	-	15.7	-	98.2	-
Gane *et al*	2014	SOF/LDV±RBV	SOF+RBV	53	35	N/A	N/A	81.1	88.6	53	28.6	35.8	0	94.3	88
Charlton *et al*	2015	SOF/LDV±RBV		105	-	68.6	-	70.7	-	66.7	-	100	-	86.7	-
Mizokami *et al*	2015	SOF/LDV±RBV		341	-	32.8	-	3.2	-	51.3	-	22.3	-	99.1	-

N/A – Data not available

Table A 2: Baseline demographics of all patients included in observational studies identified in the systematic review

Study	Year	Drug Treatment	N	Male (%)	G1a (%)	Treatment Experienced (%)	Presence of cirrhosis (%)	SVR Rate (%)
Bonnet *et al*	2014	TPV/PR	90	N/A	N/A	100	N/A	65.9
		BOC/PR	35	N/A	N/A	100	N/A	44.1
Ioannou *et al*	2014	TPV/PR	759	96	54	48	60	47.3
		BOC/PR	3696	96	60	35	29	52.2
Price *et al*	2014	TPV/PR	211	59	63	46	23	56
		BOC/PR	141	62	61	40	18	53
Colombo *et al*	2014	TPV/PR	1078	64	25.7	79.5	48.8	57
Backus *et al*	2014	TPV/PR	198	97	49	51	44	52
		BOC/PR	661	95	58	41	27	50
Bruno *et al*	2014	BOC/PR	266	68.4	20.7	100	N/A	45.9
Gordon *et al*	2015	TPV/PR	1629	60	56.1	57	39.8	54
		BOC/PR	455	62	55.8	56	30.8	44
Lebovis *et al*	2015	SOF/SMV±RBV	49	N/A	N/A	N/A	N/A	90
Backus *et al*	2015	SOF/PR	1302	95.5	61.2	37.5	38.2	66.8
		SOF/SMV±RBV	1901	95.9	59.9	36.6	63.8	75.1
Dev *et al*	2014	BOC/PR	157	68	52.9	55	26.8	78.3
Wehmeyer *et al*	2014	TPV/PR	65	66	30.8	64.6	33.8	61.5
		BOC/PR	37	54	51.4	35.1	18.9	59.5
Mauss *et al*	2014	TPV/PR	157	N/A	63.1	N/A	N/A	60.5
		BOC/PR	56	N/A	64.3	N/A	N/A	57.1
Mauss *et al*	2015	TPV/PR	800	62.4	29.3	65.9	16.6	60
		BOC/PR	287	56.4	31	51.2	12.2	53
Nazareth *et al*	2014	BOC/PR	70	N/A	N/A	86	47	57
Khalid *et al*	2013a	TPV/PR	79	62	N/A	38	N/A	81
Khalid *et al*	2013b	BOC/PR	57	57	N/A	100	N/A	57.9
Alric *et al*	2013	TPV/PR	90	N/A	N/A	100	N/A	66.7
		BOC/PR	35	N/A	N/A	100	N/A	42.9
Calleja *et al*	2015	BOC/PR	170	68.2	25	80	78	46.5
Sukeepaisarnjaroen *et al*	2015	BOC/PR	146	76	N/A	100	46	62.3
Vo *et al*	2015	TPV/PR	113	64.3	35.7	59.3	23.9	53

		BOC/PR	87	76.9	49.4	49.4	47	40
Fernandez *et al*	2014	TPV/PR	178	N/A	N/A	100	N/A	50
		BOC/PR	114	N/A	N/A	100	N/A	30.7
Petersen *et al*	2014	TPV/PR	90	N/A	N/A	N/A	N/A	62
		BOC/PR	82	N/A	N/A	N/A	N/A	57
Werner *et al*	2015	TPV/PR	102	52	27	76	28	75.5
		BOC/PR	29	69	22	69	21	62.1
Alam *et al*	2015	SOF/SMV±RBV	109	N/A	76.1	30.3	43.1	90.8
		SMV/PR	5	N/A	66.7	0	0	80
Lai *et al*	2015	SOF/PR	41	N/A	N/A	N/A	N/A	73.3
		TPV/PR	511	N/A	N/A	N/A	N/A	63
		BOC/PR	631	N/A	N/A	N/A	N/A	57.9
Fontaine *et al*	2015	DCV/SOF±RBV	84	N/A	N/A	N/A	N/A	89.3
Hezode *et al*	2013	TPV/PR	292	67.5	33.6	100	100	40
		BOC/PR	205	68.3	39.5	100	100	41
Welzel *et al*	2015	DCV/SOF±RBV	109	N/A	45.9	N/A	N/A	98.2
Foster *et al*	2015	DCV/SOF±RBV	50	N/A	N/A	N/A	N/A	88
		SOF/LDV±RBV	184	N/A	N/A	N/A	N/A	87.5
Gray *et al*	2016	TPV/PR	215	73.8	55.3	31.1	27.9	73.5
		BOC/PR	94	71.6	56.4	24.5	25.5	60.6
		SMV/PR	27	88.9	40.7	22.2	12.5	48.1
		SOF/LDV±RBV	113	64	44.2	49.5	100	85.8
		3D±RBV	58	61.8	32.8	46.2	100	91.4
Backus *et al*	2015	SOF/LDV±RBV	1831	95	76	0	35	93.6
Terrault *et al*	2015	SOF/LDV±RBV	890	61	64.7	52.9	42	96.4
Reddy *et al*	2015	SOF/SMV±RBV	136	N/A	61	63.2	100	72.1
		SOF/PR	21	N/A	47.6	66.7	100	52.4
Walker *et al*	2015	3D±RBV	44	52.3	N/A	2.3	9.1	97.7
		SOF/LDV±RBV	1663	60.2	N/A	3.5	36	95.6
Salmeron *et al*	2015	TPV/PR	652	71	21	71	50.3	65
		BOC/PR	405	65	25.2	68	53.6	52.3
Curry *et al*	2015a	SOF/LDV±RBV	632	56	67.9	0	0	95.6
Curry *et al*	2015b	SOF/LDV±RBV	476	67	67	100	100	90.3

Sulkowski *et al*	2015	SOF/SMV±RBV	836	60.9	60.9	26.8	58.7	84.2
Rodriguez *et al*	2015	SOF/SMV±RBV	20	60	55	0	100	100
Dieterich *et al*	2015	SOF/SMV±RBV	317	60	63.1	52.4	45.4	93
		SOF/PR	353	61	68	41.9	22.4	77.3
Gill *et al*	2015	SOF/LDV±RBV	91	65	61.5	46.2	50.5	82.4
Nyugen-Khac *et al*	2015	SOF/SMV±RBV	203	57	16.3	67	63.1	91.6
Roytman *et al*	2015	SOF/LDV±RBV	96	65	63.5	40.6	51	91.7

Table A 3: The Newcastle Ottawa Scale risk of bias at the outcome level for observational studies

Study	Year	Outcome	Selection				Comparability		Outcome			No. of Stars
			S1	S2	S3	S4	C1	C2	O1	O2	O3	
Bonnet *et al*	2014	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Ioannou *et al*	2014	SVR	✓	✓	✓	N/A	✓	✓	✓	✓		7
Price *et al*	2014	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Colombo *et al*	2014	SVR	✓	✓	✓	N/A			✓	✓		5
Backus *et al*	2014	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Bruno *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓		5
Gordon *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Lebovics *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓		5
Backus *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Dev *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Wehmeyer *et al*	2014	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Mauss *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Mauss *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Nazareth *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Khalid *et al*[*]	2013a	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Khalid *et al* [*]	2013b	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Alric *et al*[*]	2013	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Calleja *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Sukeepaisarnjaroen *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Vo *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓		5
Fernandez *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓		5
Petersen *et al*[*]	2014	SVR	✓	✓	✓	N/A			✓	✓		5
Warner *et al*	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Alam *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Lai *et al* [*]	2015	SVR	✓	✓	✓	N/A			✓	✓		5
Fontaine *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓		5
Hezode *et al*	2013	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Welzel *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6

Foster *et al*	2016	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Gray *et al*^	2015	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Backus *et al*	2015	SVR	✓	✓	✓	N/A	✓	✓	✓	✓		7
Terrault *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Reddy *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Walker *et al*	2015	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Salmeron *et al*	2015	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Curry *et al*[*]	2015a	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Curry *et al*[*]	2015b	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Sulkowski *et al*	2015	SVR	✓	✓	✓	N/A	✓	✓	✓	✓	✓	8
Rodriguez *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Dieterich *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Gill *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓		5
Nyugen-Khac *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓	✓	6
Roytman *et al*[*]	2015	SVR	✓	✓	✓	N/A			✓	✓		5

N/A = not applicable – outcome of interest is not a side effect

[*]Indicates this was a conference abstract identified in hand-searching of grey literature – information regarding quality was limited

[^]Indicates a study completed by the candidate. A number of abstracts have been published and one article is currently under review.

Selection contains four criteria: S1, representativeness of the exposed cohort; S2, selection of the non-exposed cohort; S3 ascertainment of exposure; S4 demonstration that outcome of interest was not present at start of study (for side effects); C1, comparability of cohorts on the basis of the design or analysis; C2, comparability of cohorts on the basis of additional factors; O1, assessment of outcome; O2 long enough follow-up for outcomes to occur; O3, adequacy of follow up of cohorts

Table A 4: Pooled SVR rates for the clinical trials and observational studies after removing studies at high risk of bias

Treatment Regimen	Study Type	n	SVR12/24 (%)	*p-value*
TPV/PR	Clinical trials	1373	67	<0.0001*
	Observational studies	2035	57	
BOC/PR	Clinical trials	1191	64	<0.0001*
	Observational studies	4997	52	
SMV/PR	Clinical trials	-	-	-
	Observational studies	27	48	
DCV/PR	Clinical trials	-	-	-
	Observational studies	-	-	
SOF/PR	Clinical trials	47	89	-
	Observational studies	-	-	
SOF+RBV	Clinical trials	72	63	-
	Observational studies	-	-	
SOF/SMV±RBV	Clinical trials	-	-	-
	Observational studies	836	84	
3D±RBV	Clinical trials	1874	96	0.653
	Observational studies	102	95	
SOF/DCV±RBV	Clinical trials	-	-	-
	Observational studies	-	-	
SOF/LDV±RBV	Clinical trials	313	93	<0.459
	Observational studies	3607	94	

*Statistically significant

Appendix 2: Propensity Scoring: Confounding Variables and Standardised Differences

Table A 5: Original confounding variables in dataset

Variable	Type	Value
Treatment experienced	Categorical	1=Yes, 0=No
Presence of cirrhosis	Categorical	1=Yes, 0=No
Age	Continuous	
BMI	Continuous	
Genotype	Categorical	1=GT1, 2=GT1a, 3=GT1b
IL28B allele	Categorical	1=CC, 2=CT, 3=TT
Baseline HCV>800,000	Categorical	1=Yes, 0=No

Table A 6: Confounding variables after inclusion of dummy variables

Variable	Type	Value
Treatment experienced	Categorical	1=Yes, 0=No
Presence of cirrhosis	Categorical	1=Yes, 0=No
Age	Continuous	
BMI	Continuous	
GT1	Categorical	1=Yes, 0=No
GT1a	Categorical	1=Yes, 0=No
IL28B CT	Categorical	1=Yes, 0=No
IL28B TT	Categorical	1=Yes, 0=No
Baseline HCV>800,000	Categorical	1=Yes, 0=No

Table A 7: Standardised difference of confounding variables between SOF/LDV±RBV and 3D±RBV patients prior to stratification

	Mean SOF/LDV±RBV	Mean 3D±RBV	Standardised Difference
Previous PI/PR experience	0.31	0.08	-0.601
Previous PR experience	0.19	0.34	0.348
Age	51.85	54.36	0.232
Sex	0.65	0.63	-0.046
GT1a	0.6	0.36	-0.492
GT1b	0.25	0.40	0.324
Baseline HCV > 800,000	0.5	0.53	0.049

PI/PR = protease inhibitor in combination with pegylated-interferon and ribavirin, PR = pegylated-interferon and ribavirin

Table A 8: Standardised difference of confounding variables between SOF/LDV±RBV and 3D±RBV patients after stratification

	Mean SOF/LDV±RBV	Mean 3D±RBV	Standardised Difference
Previous PI/PR experience	0.08	0.08	-0.009
Previous PR experience	0.34	0.34	-0.018
Age	54.02	54.36	0.032
Gender	0.67	0.63	-0.091
GT1a	0.43	0.36	-0.151*
GT1b	0.35	0.40	0.106*
Baseline HCV > 800,000	0.53	0.53	-0.10

PI/PR = protease inhibitor in combination with pegylated-interferon and ribavirin, PR = pegylated-interferon and ribavirin

*Both are above the widely accepted criterion of 0.1 but modification of the model to achieve better balance did not lead to any improvements

Appendix 3: Unit Cost Data and Sensitivity Analysis

Table A 9: Sources of unit costs

Resources	Source of unit costs
Medications (For HCV and AEs)	HSE PCRS
Staff costs*	HSE Salary Scales
Laboratory investigations	University teaching hospital laboratory/finance departments
Diagnostic investigations	University teaching hospital laboratory/finance departments
HCV-PCR assays	NVRL
Hospital admissions#	HSE-Casemix (Inpatient DRG)

HCV = hepatitis C, AEs = adverse events, HSE = Health Service Executive, PCRS = Primary Care Reimbursement Service, PCR = polymerase chain reaction, NVRL = National Virus Reference Laboratory, DRG = Diagnostic Related Group

* Median point on the relevant salary scale plus overheads, based on reported number of hours

Specific DRGs selected depending on HCV-related reason for hospital admission, cost per-diem applied based on reported length of stay

Table A 10: Resources and costs included in the estimation of the IFN-based baseline work-up

Category	Resource	Unit Cost
Staff		
	Administration	€7.15
	Phlebotomist	€1.90
	Consultant/Registrar	€26.64
	CNS	€19.11
	Pharmacist	€17.01
Labs		
	Full blood count	€16.05
	Renal	€10.03
	Coagulation	€15.29
	Liver	€10.03
	Thyroid function test	€24.07
	AFP	€15.04
	Cholesterol	€12.04
	Glucose	€3.01
	HbA1c	€20.06
	Calcium	€5.01
	Inositol Phosphate	€5.01
	Urate	€5.01
	HIV Antibodies	€10.94
	Hep A Virus	€15.45
	Hep B surface Antigen	€19.31
	Hep B surfance Antibodies	€12.67
	HCV-PCR Assay	€65.00
	Genotype	€147.54
	IL28B	€66.77
Diagnostic		
	ECG	€30.09
	CXR	€27.43

Table A 11: Resources and costs included in the estimation of the IFN-free baseline work up

Category	Resource	Unit Costs
Staff		
	Administration	€7.15
	Phlebotomist	€1.90
	Medical	€26.64
	CNS	€19.11
	Pharmacist	€17.01
Labs		
	Full blood count	€16.05
	Renal	€10.03
	Coagulation	€15.29
	Liver	€10.03
	Thyroid function tests	€24.07
	AFP	€15.04
	Cholesterol	€12.04
	Glucose	€3.01
	HbA1c	€20.06
	Calcium	€5.01
	Inositol phosphate	€5.01
	Urate	€5.01
	HIV Antibodies	€10.94
	Hep A Virus	€15.45
	Hep B surface Antigen	€19.31
	Hep B surface Antibodies	€12.67
	HCV-PCR Assay	€88.44
	Genotype	€147.54
	IL28B	€66.77
Diagnostic		
	ECG	€30.09
	CXR	€27.43
	Fibroscan	€53.00

Table A12: Costs accrued by patients in a 12-month period following achievement of a SVR12/24 excluding the cost of admissions

	IFN-based regimens	IFN-free regimens	*P*-value
Laboratory Investigations	€246 (95% CI €171-€330)	€473 (95% CI €356-€605)	<0.001
HCV-PCR Assays	€114 (95% CI €94-€136)	€295 (95% CI €242-€354)	<0.001
Diagnostic procedures	€75 (95% CI €50-€103)	€322 (95% CI €242-€354)	0.041
Referrals	€3 (95% CI €0-€10)	€67 (95% CI €19-€144)	0.002
Staff	€61 (95% CI €46-€78)	€162 (95% CI €122-€208)	<0.001
Total	€500 (95% CI €393-€617)	€1319 (95% CI €1039-€1627)	<0.001

Table A13: Comparison between the mean annual costs for untreated HCV and the mean annual costs following SVR after IFN-based treatment excluding the cost of admissions

	Mean annual costs for untreated HCV (Kieran *et al)*	Mean annual post-SVR costs following IFN-based treatment	Mean Difference	*P*-Value
F0-F3	€404 (95% CI €354-€458)	€495 (95% CI €366-€636)	€91	0.213
Compensated cirrhosis	€1762 (95% CI €974-€3229)	€521 (95% CI €308-€764)	-€1241	0.285

Table A14: Comparison between the mean annual costs for untreated HCV and the mean annual costs following SVR after IFN-free treatment excluding the cost of admissions

	Mean annual costs for untreated HCV (Kieran *et al)*	Mean annual post-SVR costs following IFN-free treatment	Mean Difference	*P*-Value
Compensated cirrhosis	€1762 (95% CI €974-€3229)	€1591 (95% CI €1243-€1947)	-€171	0.794
Decompensated cirrhosis	€6564 (95% CI €4481-€9423)	€674 (95% CI €102-€881)	-€5890	<0.001

Appendix 4: Log Odds Ratios

Table A 15: Log odds ratio and 95% CrIs for the network of RCTs only excluding observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.48	0.93
BOC/PR	1.39	0.21
SMV/PR	1.51	0.19
TPV/PR	1.41	0.17
SOF/PR	1.84	0.69
3D±RBV	4.23	0.54
PR		

Table A 16: Log odds ratio and 95% CrIs for the pooled model excluding observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.36	1.03
BOC/PR	1.46	0.35
SMV/PR	1.55	0.3
TPV/PR	1.41	0.27
SOF/PR	1.78	0.64
3D±RBV	3.84	0.57
SOF/LDV±RBV	3.84	0.7
DCV/SOF±RBV	2.42	0.79
SOF/SMV±RBV	1.86	0.52
SOF+RBV	1.14	0.90
PR		

*Not statistically significant

Table A 17: Log odds ratio and 95% CrIs for the hierarchical model excluding observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.5	0.96
BOC/PR	1.4	0.21
SMV/PR	1.52	0.19
TPV/PR	1.41	0.17
SOF/PR	1.69	0.73
3D±RBV	3.76	0.71
SOF/LDV±RBV	3.56	0.82
DCV/SOF±RBV	2.23	0.86
SOF/SMV±RBV	1.67	0.59
SOF+RBV	1.3	1.21
PR		

*Not statistically significant

Table A 18: Log odds ratio and 95% CrIs for the pooled model only including observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.47	1.01
BOC/PR	1.35	0.21
SMV/PR	1.52	0.24
TPV/PR	1.62	0.2
SOF/PR	2.24	0.44
3D±RBV	4.4	0.42
SOF/LDV±RBV	3.56	0.45
DCV/SOF±RBV	3.45	0.86
SOF/SMV±RBV	3.02	0.36
SOF+RBV	1.32	0.54
PR		

*Not statistically significant

Table A 19: Log odds ratio and 95% CrIs for the hierarchical model including observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.58	1.07
BOC/PR	1.39	0.51
SMV/PR	1.35	0.57
TPV/PR	1.71	0.43
SOF/PR	2.11	0.68
3D±RBV	4.27	0.62
SOF/LDV±RBV	3.26	0.69
DCV/SOF±RBV	3.21	1.1
SOF/SMV±RBV	2.79	0.69
SOF+RBV	1.54	0.94
PR		

*Not statistically significant

Table A 20 Log odds ratio and 95% CrIs for the hierarchical model including down-weighted observational studies

Treatment Regimen	Log Odds Ratio	Standard Deviation
DCV/PR	2.54	1.03
BOC/PR	1.36	0.39
SMV/PR	1.53	0.44
TPV/PR	1.65	0.31
SOF/PR	2.01	0.62
3D±RBV	4.36	0.55
SOF/LDV±RBV	3.14	0.69
DCV/SOF±RBV	3.24	1.02
SOF/SMV± RBV	2.85	0.59
SOF+RBV	1.48	0.81
PR		

References

1. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74.

2. Pol S, Vallet-Pichard A, Corouge M, Mallet VO. Hepatitis C: epidemiology, diagnosis, natural history and therapy. Contrib Nephrol. 2012;176:1-9.

3. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77-87.

4. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333-42.

5. Thornton L, Murphy N, Jones L, Connell J, Dooley S, Gavin S, et al. Determination of the burden of hepatitis C virus infection in Ireland. Epidemiol Infect. 2012;140(8):1461-8.

6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(4):1433-44.

7. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932-54.

8. Petta S, Cabibbo G, Enea M, Macaluso FS, Plaia A, Bruno R, et al. Personalized cost-effectiveness of boceprevir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. Dig Liver Dis. 2014;46(10):936-42.

9. Kennedy L, Craig AM. Global registries for measuring pharmacoeconomic and quality-of-life outcomes: focus on design and data collection, analysis and interpretation. Pharmacoeconomics. 2004;22(9):551-68.

10. Ades AE, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. Pharmacoeconomics. 2006;24(1):1-19.

11. Silverman SL. From randomized controlled trials to observational studies. Am J Med. 2009;122(2):114-20.

12. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet. 2008;372(9656):2152-61.

13. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. Clin Ther. 2007;29 Spec No:1284-92.

14. Marko NF, Weil RJ. The Role of Observational Investigations in Comparative Effectiveness Research. Value Health. 2010;13(8):989-97.

15. van Vollenhoven RF, Severens JL. Observational studies: a valuable source for data on the true value of RA therapies. Clin Rheumatol. 2011;30 Suppl 1:S19-24.

16. Garrison LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value Health. 2007;10(5):326-35.

17. Alter H. Discovery of non-A, non-B hepatitis and identification of its etiology. Am J Med. 1999;107(6b):16s-20s.

18. Houghton M. Discovery of the hepatitis C virus. Liver international : official journal of the International Association for the Study of the Liver. 2009;29 Suppl 1:82-8.

19. Kim CW, Chang KM. Hepatitis C virus: virology and life cycle. Clinical and molecular hepatology. 2013;19(1):17-25.

20. Shrivastava S, Mukherjee A, Ray RB. Hepatitis C virus infection, microRNA and liver disease progression. World journal of hepatology. 2013;5(9):479-86.

21. Ploss A, Dubuisson J. New advances in the molecular biology of hepatitis C virus infection: towards the identification of new treatment targets. Gut. 2012;61 Suppl 1:i25-35.

22. Ploss A, Evans MJ. Hepatitis C virus host cell entry. Curr Opin Virol. 2012;2(1):14-9.

23. Dubuisson J, Cosset FL. Virology and cell biology of the hepatitis C virus life cycle: an update. J Hepatol. 2014;61(1 Suppl):S3-s13.

24. Chevaliez S, Pawlotsky JM. HCV Genome and Life Cycle. In: Tan SL, editor. Hepatitis C Virus: Genomes and Molecular Biology. Norfolk (UK): Horizon Biosciences; 2006.

25. Liang TJ, Ghany MG. Current and Future Therapies for Hepatitis C Virus Infection. N Engl J Med. 2013;368(20):1907-17.

26. Koziel MJ. Cellular immune responses against hepatitis C virus. Clin Infect Dis. 2005;41 Suppl 1:S25-31.

27. Yang D, Liu N, Zuo C, Lei S, Wu X, Zhou F, et al. Innate host response in primary human hepatocytes with hepatitis C virus infection. PLoS One. 2011;6(11):e27552.

28. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver international : official journal of the International Association for the Study of the Liver. 2009;29 Suppl 1:89-99.

29. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. The Lancet.372(9635):321-32.

30. Santantonio T, Wiegand J, Tilman Gerlach J. Acute hepatitis C: Current status and remaining challenges. J Hepatol. 2008;49(4):625-33.

31. Chung RT. Acute hepatitis C virus infection. Clin Infect Dis. 2005;41 Suppl 1:S14-7.

32. Loomba R, Rivera MM, McBurney R, Park Y, Haynes-Williams V, Rehermann B, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. Aliment Pharmacol Ther. 2011;33(5):559-65.

33. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34-41.

34. Mohsen A, Norris S. Hepatitis C (chronic). Clin Evid (Online). 2010;2010.

35. Burns GS, Thompson AJ. Viral hepatitis B: clinical and epidemiological characteristics. Cold Spring Harb Perspect Med. 2014;4(12):a024935.

36. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014;61(1 Suppl):S58-68.

37. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol. 2012;26(4):401-12.

38. Thomas DL. Global control of hepatitis C: where challenge meets opportunity. Nat Med. 2013;19(7):850-8.

39. Massard J, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, et al. Natural history and predictors of disease severity in chronic hepatitis C. J Hepatol. 2006;44(1 Suppl):S19-24.

40. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-31.

41. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349(9055):825-32.

42. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529-38.

43. Tran TT. Overview of epidemiology, diagnosis, and disease progression associated with hepatitis C. Am J Manag Care. 2012;18(14 Suppl):S335-9.

44. Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clin Infect Dis. 2012;55 Suppl 1:S10-5.

45. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol. 2013;58(3):593-608.

46. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.

47. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology. 1997;26(S3):34S-8S.

48. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132(7):2557-76.

49. Gonzalez-Moreno J, Payeras-Cifre A. Hepatitis C virus infection: looking for interferon free regimens. ScientificWorldJournal. 2013;2013:825375.

50. Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014;59(1):318-27.

51. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-57.

52. WHO. Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection. 2014.Report

53. Andriulli A, Morisco F, Ippolito AM, Di Marco V, Valvano MR, Angelico M, et al. HCV genotype 1 subtypes (1a and 1b): similarities and differences in clinical features and therapeutic outcome. Hepatol Int. 2015;9(1):52-7.

54. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007;13(17):2436-41.

55. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011;17(2):107-15.

56. Lee MH, Yang HI, Yuan Y, L'Italien G, Chen CJ. Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol. 2014;20(28):9270-80.

57. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nature reviews Gastroenterology & hepatology. 2013;10(9):553-62.

58. Negro F. Epidemiology of hepatitis C in Europe. Dig Liver Dis. 2014;46 Suppl 5:S158-64.

59. HPSC. Infectious Disease Notification in Ireland, 2004-2014, CIDR Ireland2015 [3rd May 2016]. Available from: http://www.hpsc.ie/NotifiableDiseases/AnnualIDStatistics/File,2393,en.pdf

60. Smyth BP, Keenan E, O'Connor JJ. Bloodborne viral infection in Irish injecting drug users. Addiction. 1998;93(11):1649-56.

61. Smyth BP, Keenan E, O'Connor JJ. Evaluation of the impact of Dublin's expanded harm reduction programme on prevalence of hepatitis C among short-term injecting drug users. J Epidemiol Community Health. 1999;53(7):434-5.

62. Smyth R, Keenan E, Dorman A, O'Connor J. Hepatitis C infection among injecting drug users attending the National Drug Treatment Centre. Ir J Med Sci. 1995;164(4):267-8.

63. Grogan L, Tiernan M, Geogeghan N, Smyth B, Keenan E. Bloodborne virus infections among drug users in Ireland: a retrospective cross-sectional survey of screening, prevalence, incidence and hepatitis B immunisation uptake. Ir J Med Sci. 2005;174(2):14-20.

64. Allwright S, Bradley F, Long J, Barry J, Thornton L, Parry JV. Prevalence of antibodies to hepatitis B, hepatitis C, and HIV and risk factors in Irish prisoners: results of a national cross sectional survey. BMJ. 2000;321(7253):78-82.

65. Cullen W, Bury G, Barry J, O'Kelly F. Drug users attending general practice in Eastern Regional Health Authority (ERHA) area. Ir Med J. 2000;93(7):214-7.

66. Cullen W, Bury G, Barry J, O'Kelly FD. Hepatitis C infection among drug users attending general practice. Ir J Med Sci. 2003;172(3):123-7.

67. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med. 1999;340(16):1228-33.

68. Smith DB, Lawlor E, Power J, O'Riordan J, McAllister J, Lycett C, et al. A second outbreak of hepatitis C virus infection from anti-D immunoglobulin in Ireland. Vox Sang. 1999;76(3):175-80.

69. Wedemeyer H, Dore GJ, Ward JW. Estimates on HCV disease burden worldwide - filling the gaps. J Viral Hepat. 2015;22 Suppl 1:1-5.

70. Sibley A, Han KH, Abourached A, Lesmana LA, Makara M, Jafri W, et al. The present and future disease burden of hepatitis C virus infections with today's treatment paradigm - volume 3. J Viral Hepat. 2015;22 Suppl 4:21-41.

71. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clin Infect Dis. 2011;53(2):150-7.

72. Alfaleh FZ, Nugrahini N, Maticic M, Tolmane I, Alzaabi M, Hajarizadeh B, et al. Strategies to manage hepatitis C virus infection disease burden - volume 3. J Viral Hepat. 2015;22 Suppl 4:42-65.

73. Gane E, Kershenobich D, Seguin-Devaux C, Kristian P, Aho I, Dalgard O, et al. Strategies to manage hepatitis C virus (HCV) infection disease burden - volume 2. J Viral Hepat. 2015;22 Suppl 1:46-73.

74. Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 2. J Viral Hepat. 2015;22 Suppl 1:26-45.

75. Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014;21 Suppl 1:34-59.

76. Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat G, et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat. 2014;21 Suppl 1:60-89.

77. Chhatwal J, Wang X, Ayer T, Kabiri M, Chung RT, Hur C, et al. Hepatitis C Disease Burden in the United States in the Era of Oral Direct-Acting Antivirals. Hepatology. 2016.

78. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. 2013;57(6):2164-70.

79. Patruni B, Nolte E. Hepatitis C: A Projection of the Healthcare and Economic Burden in the UK. 2013.Report

80. NCRI. National Cancer Registry Ireland Incidence Statistics 2016 [cited 2016 27th May]. Available from: http://www.ncri.ie/data/incidence-statistics

81. Kieran J, Norris S, O'Leary A, Walsh C, Merriman R, Houlihan D, et al. Hepatitis C in the era of direct-acting antivirals: real-world costs of untreated chronic hepatitis C; a cross-sectional study. BMC Infect Dis. 2015;15(471).

82. Kieran J, Bennett K, Coghlan M, Bergin C, Barry M. The Budget Impact of Hepatitis C Treatment in Ireland 2001-2012. Ir Med J. 2015;108(6):166-9.

83. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144(7):1450-5.e2.

84. Yoshida EM, Sulkowski MS, Gane EJ, Herring RW, Ratziu V, Ding X, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology. 2015;61(1):41-5.

85. Hayashi N, Takehara T. Antiviral therapy for chronic hepatitis C: past, present, and future. J Gastroenterol. 2006;41(1):17-27.

86. Lange CM, Jacobson IM, Rice CM, Zeuzem S. Emerging therapies for the treatment of hepatitis C. EMBO Mol Med. 2014;6(1):4-15.

87. Heim MH. 25 years of interferon-based treatment of chronic hepatitis C: an epoch coming to an end. Nat Rev Immunol. 2013;13(7):535-42.

88. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. BMJ. 2014;348:g3308.

89. Alexopoulou A, Papatheodoridis GV. Current progress in the treatment of chronic hepatitis C. World J Gastroenterol. 2012;18(42):6060-9.

90. Doyle JS, Aspinall E, Liew D, Thompson AJ, Hellard ME. Current and emerging antiviral treatments for hepatitis C infection. Br J Clin Pharmacol. 2013;75(4):931-43.

91. Rosen HR. Clinical practice. Chronic hepatitis C infection. N Engl J Med. 2011;364(25):2429-38.

92. Smith KR, Suppiah V, O'Connor K, Berg T, Weltman M, Abate ML, et al. Identification of improved IL28B SNPs and haplotypes for prediction of drug response in treatment of hepatitis C using massively parallel sequencing in a cross-sectional European cohort. Genome Med. 2011;3(8):57.

93. Matsuura K, Watanabe T, Tanaka Y. Role of IL28B for chronic hepatitis C treatment toward personalized medicine. J Gastroenterol Hepatol. 2014;29(2):241-9.

94. Nguyen CM, Mendes M, Tsunoda S, Ma JD. Interleukin-28B genotype testing to determine response to the combination of pegylated-interferon and ribavirin for the treatment of hepatitis C virus. PLoS currents. 2011;3:Rrn1207.

95. Rosso C, Abate ML, Ciancio A, Strona S, Caviglia GP, Olivero A, et al. IL28B polymorphism genotyping as predictor of rapid virologic response during interferon plus ribavirin treatment in hepatitis C virus genotype 1 patients. World J Gastroenterol. 2014;20(36):13146-52.

96. Martinello M, Dore GJ. Editorial Commentary: Interferon-free Hepatitis C Treatment Efficacy From Clinical Trials Will Translate to "Real World" Outcomes. Clin Infect Dis. 2016;62(7):927-8.

97. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24.

98. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2417-28.

99. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16.

100. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010;362(14):1292-303.

101. Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009;360(18):1839-50.

102. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827-38.

103. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195-206.

104. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 2010;376(9742):705-16.

105. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1207-17.

106. Belousova V, Abd-Rabou AA, Mousa SA. Recent advances and future directions in the management of hepatitis C infections. Pharmacol Ther. 2014.

107. Clark VC, Peter JA, Nelson DR. New therapeutic strategies in HCV: second-generation protease inhibitors. Liver international : official journal of the International Association for the Study of the Liver. 2013;33 Suppl 1:80-4.

108. Maasoumy B, Port K, Markova AA, Serrano BC, Rogalska-Taranta M, Sollik L, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. PLoS One. 2013;8(2):e55285.

109. Schiffman ML. The New Antivirals in HCV Infection: Candidates for Triple Therapy Medscape Multispeciality2012 [cited 2016 May 25th]. Available from: http://www.medscape.org/viewarticle/766107

110. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): A phase 3, randomised, double-blind, placebo-controlled trial. The Lancet. 2014;384(9941):403-13.

111. Manns M, Marcellin P, Poordad F, De Araujo ESA, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2014;384(9941):414-26.

112. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. Gastroenterology. 2014;146(7):1669-79.e3.

113. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014;146(2):430-41.e6.

114. Flisiak R, Jaroszewicz J, Parfieniuk-Kowerda A. Emerging treatments for hepatitis C. Expert opinion on emerging drugs. 2013;18(4):461-75.

115. Dore GJ, Lawitz E, Hezode C, Shafran SD, Ramji A, Tatum HA, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. Gastroenterology. 2015;148(2):355-66.e1.

116. Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: A randomised, double-blind, phase 2 trial. The Lancet Infectious Diseases. 2013;13(5):401-8.

117. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, Demicco M, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): An open-label, randomised, multicentre phase 2 trial. The Lancet. 2013;381(9883):2100-7.

118. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878-87.

119. deLemos AS, Chung RT. Hepatitis C treatment: an incipient therapeutic revolution. Trends Mol Med. 2014;20(6):315-21.

120. Afdhal NH, Zeuzem S, Schooley RT, Thomas DL, Ward JW, Litwin AH, et al. The new paradigm of hepatitis C therapy: integration of oral therapies into best practices. J Viral Hepat. 2013;20(11):745-60.

121. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013;310(8):804-11.

122. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015;63(1):199-236.

123. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: The COSMOS randomised study. The Lancet. 2014;384(9956):1756-65.

124. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211-21.

125. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889-98.

126. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483-93.

127. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370(20):1879-88.

128. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1594-603.

129. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1604-14.

130. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370(21):1973-82.

131. AASLD. Recommendations for the Testing, Managing and Treating Hepatitis C. USA: AASLD and IDSA, 2016.http://hcvguidelines.org/sites/default/files/HCV-Guidance_January_2016_c7.pdf.Report

132. Alric L, Bonnet D. Grazoprevir + elbasvir for the treatment of hepatitis C virus infection. Expert Opin Pharmacother. 2016;17(5):735-42.

133. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1075-86.

134. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. The lancet HIV. 2015;2(8):e319-27.

135. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H, Jr., et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with

hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537-45.

136. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1087-97.

137. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015;373(27):2599-607.

138. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med. 2015;373(27):2618-28.

139. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015;373(27):2608-17.

140. Solomon M, Bonafede M, Pan K, Wilson K, Beam C, Chakravarti P, et al. Direct medical care costs among pegylated interferon plus ribavirin-treated and untreated chronic hepatitis C patients. Dig Dis Sci. 2011;56(10):3024-31.

141. Stahmeyer JT, Krauth C, Bert F, Pfeiffer-Vornkahl H, Alshuth U, Huppe D, et al. Costs and outcomes of treating chronic hepatitis C patients in routine care - results from a nationwide multicenter trial. J Viral Hepat. 2016;23(2):105-15.

142. Thomas DL. Advances in the treatment of hepatitis C virus infection. Top Antivir Med. 2012;20(1):5-10.

143. NCPE. Economic evaluation of Telaprevir (Incivo®) as add-on therapy to pegylated interferon and ribavirin for the treatment of patients infected with Hepatitis C Genotype 1. 2012.Report

144. NCPE. Cost-effectiveness of boceprevir (Victrelis®) for the treatment of patients infected with genotype 1 hepatitis C virus in the Irish healthcare setting. 2012.Report

145. Deuffic-Burban S, Yazdanpanah Y. Fair prices for new direct-acting antiviral agents (DAAs) to make treatment for all affordable. Gut. 2015.

146. NCPE. Cost effectiveness of sofosbuvir (in combination with either ribavirin or pegylated interferon + ribavirin) (Sovaldi®) for the treatment of hepatitis C infection. National Centre for Pharmacoeconomics, 2014.Report

147. Drummond M, Schulpher M, Torrence G, O'Brien J, Stoddart G. Methods for the economic evaluation of health care programmes. 3rd ed. New York: Oxford University Press; 2005.

148. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. Pharmacoeconomics. 2008;26(2):131-48.

149. HIQA. Guidelines for the Economic Evaluation of Health Technologies in Ireland. Health Information and Quality Authority, 2014.Report

150. Saramago P, Manca A, Sutton AJ. Deriving input parameters for cost-effectiveness modeling: taxonomy of data types and approaches to their statistical synthesis. Value Health. 2012;15(5):639-49.

151. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006;15(7):677-87.

152. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ. 2004;13(5):405-15.

153. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: OUP Oxford; 2006.

154. IPHA, HSE. IPHA-HSE Agreement on the Supply of Medicines to the Health Services 2012. 2012.http://www.ipha.ie/alist/ipha-hse-agreement.aspx.Report

155. Tilson L, Barry M. Recent developments in pharmacoeconomic evaluation in Ireland. Expert Rev Pharmacoecon Outcomes Res. 2010;10(3):221-4.

156. Tilson L, O'Leary A, Usher C, Barry M. Pharmacoeconomic evaluation in Ireland: a review of the process. Pharmacoeconomics. 2010;28(4):307-22.

157. Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013;59(3):434-41.

158. Vandijck D, Starkel P. Innovative strategies for hepatitis C in Belgium integrating treatment efficacy, public disease burden, and healthcare costs. Acta Gastroenterol Belg. 2014;77(2):274-6.

159. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane database of systematic reviews. 2014(4):Mr000034.

160. Fleurence RL, Naci H, Jansen JP. The critical role of observational evidence in comparative effectiveness research. Health Aff (Millwood). 2010;29(10):1826-33.

161. Dreyer NA, Tunis SR, Berger M, Ollendorf D, Mattox P, Gliklich R. Why observational studies should be among the tools used in comparative effectiveness research. Health Aff (Millwood). 2010;29(10):1818-25.

162. Kendall JM. Designing a research project: randomised controlled trials and their principles. Emerg Med J. 2003;20(2):164-8.

163. Dowd R, Recker RR, Heaney RP. Study subjects and ordinary patients. Osteoporos Int. 2000;11(6):533-6.

164. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med. 2002;162(15):1682-8.

165. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305-10.

166. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.

167. Carlson MD, Morrison RS. Study design, precision, and validity in observational studies. J Palliat Med. 2009;12(1):77-82.

168. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359(9302):248-52.

169. Berger ML, Mamdani M, Atkins D, Johnson ML. Good Research Practices for Comparative Effectiveness Research: Defining, Reporting and Interpreting Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. Value Health.12(8):1044-52.

170. Booth CM, Tannock IF. Evaluation of treatment benefit: randomized controlled trials and population-based observational research. J Clin Oncol. 2013;31(26):3298-9.

171. Ray JG. Evidence in upheaval: incorporating observational data into clinical practice. Arch Intern Med. 2002;162(3):249-54.

172. Lecky FE, Driscoll PA. The clinical relevance of observational research. J Accid Emerg Med. 1998;15(3):142-6.

173. Boyko EJ. Observational research--opportunities and limitations. J Diabetes Complications. 2013;27(6):642-8.

174. Lindor RA, Lindor KD. The value of observational research in liver diseases. Hepatology. 2011;53(1):1-3.

175. Chang TI, Winkelmayer WC. Comparative effectiveness research: what is it and why do we need it in nephrology? Nephrol Dial Transplant. 2012;27(6):2156-61.

176. Seida J, Dryden DM, Hartling L. The value of including observational studies in systematic reviews was unclear: a descriptive study. J Clin Epidemiol. 2014;67(12):1343-52.

177. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60.

178. Greenfield S, Platt R. Can observational studies approximate RCTs? Value Health. 2012;15(2):215-6.

179. Starks H, Diehr P, Curtis JR. The challenge of selection bias and confounding in palliative care research. J Palliat Med. 2009;12(2):181-7.

180. Henderson M, Page L. Appraising the evidence: what is selection bias? Evidence-based mental health. 2007;10(3):67-8.

181. Austin PC, Platt RW. Survivor treatment bias, treatment selection bias, and propensity scores in observational research. J Clin Epidemiol. 2010;63(2):136-8.

182. Coggon D, Barker D, Rose G. Measurement of Error and Bias. In: Journal BM, editor. Epidemiology for the Uninitiatied2003.

183. Ellenberg JH. Selection bias in observational and experimental studies. Stat Med. 1994;13(5-7):557-67.

184. Quartey G, Feudjo-Tepie M, Wang J, Kim J. Opportunities for minimization of confounding in observational research. Pharm Stat. 2011;10(6):539-47.

185. Wunsch H, Linde-Zwirble WT, Angus DC. Methods to adjust for bias and confounding in critical care health services research involving observational data. J Crit Care. 2006;21(1):1-7.

186. Hammer GP, du Prel J-B, Blettner M. Avoiding bias in observational studies. Dtsch Arzteblatt Int. 2009;106:664-8.

187. Jepsen P, Johnsen SP, Gillman MW, Sørensen HT. Interpretation of observational studies. Heart. 2004;90(8):956-60.

188. Delgado-Rodriguez M, Llorca J. Bias. J Epidemiol Community Health. 2004;58(8):635-41.

189. Fiellin DA, Samet JH, O'Connor PG. Reducing Bias in Observational Research on Alcohol Withdrawal Syndrome. Subst Abus. 1998;19(1):23-31.

190. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg. 2010;126(6):2234-42.

191. Woodward M. Epidemiology: study design and data analysis: CRC press; 2013.

192. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet. 2002;359(9303):341-5.

193. Briggs AH, Levy AR. Pharmacoeconomics and pharmacoepidemiology: curious bedfellows or a match made in heaven? Pharmacoeconomics. 2006;24(11):1079-86.

194. Sedgwick P. Cross sectional studies: advantages and disadvantages2014 2014-03-26 11:58:40.

195. Levin KA. Study design III: Cross-sectional studies. Evidence-based dentistry. 2006;7(1):24-5.

196. Sedgwick P. Bias in observational study designs: cross sectional studies. BMJ. 2015;350:h1286.

197. Pandis N. Case-control studies: part 2. Am J Orthod Dentofacial Orthop. 2014;146(3):402-3.

198. Newgard CD, Hedges JR, Arthur M, Mullins RJ. Advanced statistics: the propensity score--a method for estimating treatment effect in observational research. Acad Emerg Med. 2004;11(9):953-61.

199. Morshed S, Tornetta P, 3rd, Bhandari M. Analysis of observational studies: a guide to understanding statistical methods. J Bone Joint Surg Am. 2009;91 Suppl 3:50-60.

200. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150-61.

201. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med. 2008;27(12):2037-49.

202. Guo S, Fraser MW. Propensity Score Analysis: Statistical Methods and Applications: Statistical Methods and Applications: Sage Publications; 2014.

203. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research. 2011;46(3):399-424.

204. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making. 2009;29(6):661-77.

205. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. Stat Med. 2010;29(20):2137-48.

206. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg. 2007;134(5):1128-35.

207. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annu Rev Public Health. 2000;21:121-45.

208. Deb S, Austin PC, Tu JV, Ko DT, Mazer CD, Kiss A, et al. A Review of Propensity-Score Methods and Their Use in Cardiovascular Research. Can J Cardiol. 2016;32(2):259-65.

209. Rubin DB. On principles for modeling propensity scores in medical research. Pharmacoepidemiol Drug Saf. 2004;13(12):855-7.

210. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J. 2011;32(14):1704-8.

211. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med. 2013;32(16):2837-49.

212. Austin PC. A Tutorial and Case Study in Propensity Score Analysis: An Application to Estimating the Effect of In-Hospital Smoking Cessation Counseling on Mortality. Multivariate behavioral research. 2011;46(1):119-51.

213. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf. 2008;17(12):1202-17.

214. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17(19):2265-81.

215. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. Stat Med. 2006;25(12):2084-106.

216. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med. 2007;26(4):734-53.

217. Austin PC. Type I Error Rates, Coverage of Confidence Intervals, and Variance Estimation in Propensity-Score Matched Analyses. The International Journal of Biostatistics. 2009;5(1):13.

218. Arnaud C, Trepo C, Petit MA. Predictors of the therapeutic response in hepatitis C. A 2013 update. Clinics and research in hepatology and gastroenterology. 2013.

219. Beinhardt S, Rutter K, Stattermayer AF, Ferenci P. Revisiting the predictors of a sustained virologic response in the era of direct-acting antiviral therapy for hepatitis C virus. Clin Infect Dis. 2013;56(1):118-22.

220. Cavalcante LN, Lyra AC. Predictive factors associated with hepatitis C antiviral therapy response. World journal of hepatology. 2015;7(12):1617-31.

221. Petta S, Craxi A. How to optimize HCV therapy in genotype 1 patients: predictors of response. Liver international : official journal of the International Association for the Study of the Liver. 2013;33 Suppl 1:23-9.

222. Poordad F, Bronowicki J, Gordon SC, Zeuzem S, Jacobson IM, Sulkowski MS, et al. Factors that predict response of patients with hepatitis C virus infection to Boceprevir. Gastroenterology. 2012;143(3):608-18.e5.

223. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics. 1996;52(1):249-64.

224. Caliendo M, Kopeinig S. Some Practical Guidance for the Implementation of Propensity Score Matching 2005 7th December 2016. Available from: http://ftp.iza.org/dp1588.pdf.

225. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

226. Gliklich RE, Dreyer NA. AHRQ Methods for Effective Health Care. Registries for Evaluating Patient Outcomes: A User's Guide. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010.

227. Harpe SE. Using secondary data sources for pharmacoepidemiology and outcomes research. Pharmacotherapy. 2009;29(2):138-53.

228. Norris CM, Ghali WA, Knudtson ML, Naylor CD, Saunders LD. Dealing with missing data in observational health care outcome analyses. J Clin Epidemiol. 2000;53(4):377-83.

229. Soley-Bori M. Dealing with missing data: Key assumptions and methods for applied analysis. Boston University School of Public Health 2013.Report

230. Harel O, Zhou XH. Multiple imputation: review of theory, implementation and software. Stat Med. 2007;26(16):3057-77.

231. Little RJA, Rubin D. Statistical analysis with missing data. New York: John Wiley & Sons; 2002.

232. Rubin D. Multiple Imputation for Non Response in Survey. New York: John Wiley & Sons; 1987.

233. McCleary L. Using multiple imputation for analysis of incomplete data in clinical research. Nurs Res. 2002;51(5):339-43.

234. Silman A. Use of whole population registers: advantages and disadvantages. Bull NYU Hosp Jt Dis. 2007;65(2):143-5.

235. Dreyer NA, Garner S. Registries for robust evidence. JAMA. 2009;302(7):790-1.

236. Shah BR, Drozda J, Peterson ED. Leveraging observational registries to inform comparative effectiveness research. Am Heart J. 2010;160(1):8-15.

237. Krumholz HM. Outcomes research: generating evidence for best practice and policies. Circulation. 2008;118(3):309-18.

238. Lecluse L, Naldi L, Stern R, Spuls P. National registries of systemic treatment for psoriasis and the European 'Psonet'initiative. Dermatology. 2008;218(4):347-56.

239. Rabeneck L, Menke T, Simberkoff MS, Hartigan PM, Dickinson GM, Jensen PC, et al. Using the national registry of HIV-infected veterans in research: lessons for the development of disease registries. J Clin Epidemiol. 2001;54(12):1195-203.

240. Jones S, James E, Prasad S. Disease registries and outcomes research in children: focus on lysosomal storage disorders. Paediatr Drugs. 2011;13(1):33-47.

241. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312(7023):71-2.

242. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis: techniques and a guide for the academic surgeon. Annals of cardiothoracic surgery. 2015;4(2):112-22.

243. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000;342(25):1887-92.

244. Golden SH, Bass EB. Validity of meta-analysis in diabetes: meta-analysis is an indispensable tool in evidence synthesis. Diabetes Care. 2013;36(10):3368-73.

245. Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. Evidence synthesis for decision making 7: a reviewer's checklist. Med Decis Making. 2013;33(5):679-91.

246. Sutton AJ, Cooper NJ, Jones DR. Evidence synthesis as the key to more coherent and efficient research. BMC Med Res Methodol. 2009;9:29.

247. Teutsch SM, Berger ML. Evidence synthesis and evidence-based decision making: related but distinct processes. Med Decis Making. 2005;25(5):487-9.

248. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med. 1997;126(5):376-80.

249. Newhouse RP. Evidence synthesis: the good, the bad, and the ugly. J Nurs Adm. 2008;38(3):107-11.

250. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011;14(4):417-28.

251. Schmitz S, Adams R, Walsh CD, Barry M, FitzGerald O. A mixed treatment comparison of the efficacy of anti-TNF agents in rheumatoid arthritis for methotrexate non-responders demonstrates differences between treatments: a Bayesian approach. Ann Rheum Dis. 2012;71(2):225-30.

252. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health. 2008;11(5):956-64.

253. Kieran J, Schmitz S, O'Leary A, Walsh C, Bergin C, Norris S, et al. The relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1. Clin Infect Dis. 2013;56(2):228-35.

254. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315(7121):1533-7.

255. Sutton AJ, Abrams KR, Jones DR. An illustrated guide to the methods of meta-analysis. J Eval Clin Pract. 2001;7(2):135-48.

256. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683-91.

257. EUnetHTA. Comparators and Comparisons: Direct and indirect comparisions. EUnetHTA, 2015.http://eunethta.eu/outputs/comparators-comparisons-direct-and-indirect-comparisons-amended-ja1-guideline-final-nov-2015.Report

258. Panagiotou OA. Network Meta-Analysis: Evidence Synthesis With Mixed Treatment Comparison. Am J Epidemiol. 2015.

259. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Stat Med. 2007;26(6):1237-54.

260. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.

261. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med. 2011;9(1):1-5.

262. Caldwell DM. An overview of conducting systematic reviews with network meta-analysis. Systematic reviews. 2014;3:109.

263. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013;33(5):641-56.

264. Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford). 2007;46(7):1140-7.

265. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess

relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17(2):157-73.

266. FDA. Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Maryland, USA: Food and Drug Administration, 2013.http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.Report

267. Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed treatment comparison model. Stat Med. 2013;32(17):2935-49.

268. Sutton AJ, Higgins JP. Recent developments in meta-analysis. Stat Med. 2008;27(5):625-50.

269. Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. Stat Med. 2000;19(24):3359-76.

270. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105-24.

271. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics. 2008;26(9):753-67.

272. O'Rourke K, Walsh C, Hutchinson M. Outcome of beta-interferon treatment in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol. 2007;254(11):1547-54.

273. Dreyer NA. GRACE: Good Research for Comparative Effectiveness. 2010.Report

274. Dreyer NA, Schneeweiss S, McNeil BJ, Berger ML, Walker AM, Ollendorf DA, et al. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. Am J Manag Care. 2010;16(6):467-71.

275. Koh C, Zhao X, Samala N, Sakiani S, Liang TJ, Talwalkar JA. AASLD clinical practice guidelines: a critical review of scientific evidence and evolving recommendations. Hepatology. 2013;58(6):2142-52.

276. EASL Clinical Practice Guidelines: Management of hepatits C virus infection. J Hepatol. 2014;60:392-420.

277. Ibargoyen-Roteta N, Cabriada-Nuno JL, Gutierrez-Ibarluzea I, Hernandez-Ramirez V, Clofent-Vilaplana J, Domenech-Morral E, et al. Post-marketing health technology monitoring. The analysis of an experience from a clinical perspective. Front Pharmacol. 2011;2:45.

278. ENCePP. Guide on Methodological Standards in Pharmacoepidemiology. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2016.http://www.encepp.eu/standards_and_guidances.Report

279. Van den Broeck J, Cunningham SA, Eeckels R, Herbst K. Data cleaning: detecting, diagnosing, and editing data abnormalities. PLoS Med. 2005;2(10):e267.

280. Li T, Hutfless S, Scharfstein DO, Daniels MJ, Hogan JW, Little RJA, et al. Standards should be applied in the prevention and handling of missing data for patient-centered outcomes research: a systematic review and expert consensus. J Clin Epidemiol. 2014;67(1):15-32.

281. von Elm E, Altman DG, Pocock S, Vandenbroucke JP, Egger M. Re: "quality of reporting of observational longitudinal research". Am J Epidemiol. 2005;162(10):1032-3; author reply 3.

282. Shea M, Ostermann L, Hohman R, Roberts S, Kozak M, Dull R, et al. Regulatory Watch: Impact of breakthrough therapy designation on cancer drug development. Nature reviews Drug discovery. 2016;15(3):152.

283. Chizkov RR, Million RP. Trends in breakthrough therapy designation. Nature reviews Drug discovery. 2015;14(9):597-8.

284. Saeed S, Strumpf EC, Walmsley SL, Rollet-Kurhajec K, Pick N, Martel-Laferriere V, et al. How Generalizable Are the Results From Trials of Direct Antiviral Agents to People Coinfected With HIV/HCV in the Real World? Clin Infect Dis. 2016;62(7):919-26.

285. Schumock GT, Pickard AS. Comparative effectiveness research: Relevance and applications to pharmacy. Am J Health Syst Pharm. 2009;66(14):1278-86.

286. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Clin Epidemiol. 2009;62(5):499-505.

287. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.

288. Mathes T, Antoine SL, Pieper D. Factors influencing adherence in Hepatitis-C infected patients: a systematic review. BMC Infect Dis. 2014;14:203.

289. Dieterich DT, Bacon B, Flamm SL, Kowdley K, Milligan S, Tsai N, et al. Final evaluation of 955 HCV patients treated with 12 week regimens containing sofosbuvir +/- simeprevir in the trio network: Academic and community treatment of a real-world, heterogeneous population. Gastroenterology. 2015;148(4):S1001.

290. Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: Real world experience from HCV-TARGET. J Hepatol. 2015;62(2):286-93.

291. Gray E, O'Leary A, Walsh C, Bergin CJ, Norris S. Outcomes from the Irish national hepatitis C prospective treatment registry. Hepatology. 2014;60:689A-90A.

292. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.

293. Aslam S, Emmanuel P. Formulating a researchable question: A critical step for facilitating good clinical research. Indian Journal of Sexually Transmitted Diseases and AIDS. 2010;31(1):47.

294. Higgins J, Green S. The Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd; 2011. Available from: http://www.cochrane-handbook.org.

295. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses Ottawa, Ontario, Canada: The Ottawa Hospital Research Institute; [cited 2016 11th March]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

296. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.

297. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14(1):1-5.

298. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained

virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014;147(2):359-65.e1.

299. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370(21):1983-92.

300. Flamm SL, Lawitz E, Jacobson I, Bourliere M, Hezode C, Vierling JM, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. Clin Gastroenterol Hepatol. 2013;11(1):81-7.e4; quiz e5.

301. Pol S, Ghalib RH, Rustgi VK, Martorell C, Everson GT, Tatum HA, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: A randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. The Lancet Infectious Diseases. 2012;12(9):671-7.

302. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014;146(3):736-43.e1.

303. Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015;15(6):645-53.

304. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown Jr RS, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015;149(3):649-59.

305. Bourliere M, Bronowicki JP, de Ledinghen V, Hezode C, Zoulim F, Mathurin P, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: A randomised, double-blind, phase 2 trial (SIRIUS). The Lancet Infectious Diseases. 2015;15(4):397-404.

306. Dore GJ, Conway B, Luo Y, Janczewska E, Knysz B, Liu Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: The MALACHITE-I/II trials. J Hepatol. 2016;64(1):19-28.

307. Lalezari J, Nelson D, Hyland RH, Lin M, Rossi S, Symonds W, et al. Once daily sofosbuvir plus ribavirin for 12 weeks and 24 weeks in treatment-naive patients with HCV infection: The Quantum Study. J Hepatol. 2013;58(S1):S346.

308. Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology. 2013;58(6):1918-29.

309. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014;370(3):222-32.

310. Lawitz E, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, et al. A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir (SMV) plus sofosbuvir (SOF) in treatment-naive or -experienced pateints with chronic HCV genotype 1 infection and cirrhosis: OPTIMIST-2. J Hepatol. 2015;62(S1):S264.

311. Kwo P, Gitlin N, Nahass R, Bernstein D, Rojter S, Schiff E, et al. A phase 3, randomised, open-label study to evaluate the efficacy and safety of 8 and 12 weeks of simeprevir (SMV) plus sofosbuvir (SOF) in treatment naive and -experienced patients with chronic HCV genotype 1 infection without cirrhosis: Optimist 1. J Hepatol. 2015;62(S1):S270.

312. Reddy KR, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C, et al. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): A randomised, double-blind, non-inferiority phase 3 trial. The Lancet Infectious Diseases. 2015;15(1):27-35.

313. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): An open-label, randomised, phase 2 trial. The Lancet. 2014;383(9916):515-23.

314. Chulanov V, Zhdanov K, Kersey K, Zhu Y, Massetto B, Zhuravel S, et al. Sofosbuvir plus Ribavirin for the Treatment of Russian Patients with Chronic HCV Genotype 1 or 3 Infection. Hepatology. 2014;60(4S):676A.

315. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84.

316. Alam I, Manch R, Naggie S, Reindollar R, Slim J, Prabhakar A, et al. Effectiveness of simeprevir (SMV)-containing regimens among patients with chronic hepatitis C virus (HCV) in various us practice settings: Interim analysis of the SONET study. J Hepatol. 2015;62:S646-S7.

317. Alric L, Guivarch M, Berard E, Metivier S, Barange K, Nicot F, et al. Sustained virological response to telaprevir and boceprevir in previously non-responder HCV genotype 1 patients with severe liver fibrosis: Results of a prospective multi-centric study. Hepatology. 2013;58(4 Supp):1155A.

318. Backus LI, Belperio PS, Shahoumian TA, Cheung R, Mole LA. Comparative effectiveness of the hepatitis C virus protease inhibitors boceprevir and telaprevir in a large U.S. cohort. Aliment Pharmacol Ther. 2014;39(1):93-103.

319. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans. Aliment Pharmacol Ther. 2015.

320. Backus LI, Belperio PS, Shahoumian T, Loomis TP, Mole LA. Effectiveness of ledipasvir/sofosbuvir in treatment naïve genotype 1 patients treated in routine medical practice. Hepatology. 2015;62:255A-6A.

321. Bonnet D, Guivarch M, Berard E, Combis JM, Remy AJ, Glibert A, et al. Telaprevir- and boceprevir-based tritherapies in real practice for F3-F4 pretreated hepatitis C virus patients. World journal of hepatology. 2014;6(9):660-9.

322. Bruno S, Bollani S, Zignego AL, Calvaruso V, Magni C, Landonio S, et al. Efficacy and safety of boceprevir-based therapy in HCVG1 treatment-experienced patients with advanced fibrosis/cirrhosis: Italian NPP survey. Dig Liver Dis. 2014;46:e12.

323. Calleja JL, Pascasio JM, Ruiz-Antoran B, Gea F, Barcena R, Larrubia JR, et al. Safety and efficacy of triple therapy with peginterferon, ribavirin and boceprevir within an early access programme in Spanish patients with hepatitis C genotype 1 with severe fibrosis: SVRw12 analysis. Liver international : official journal of the International Association for the Study of the Liver. 2015;35(1):90-100.

324. Colombo M, Strasser S, Moreno C, Abrao Ferreira P, Urbanek P, Fernandez I, et al. Sustained virological response with telaprevir in 1078 patients with advanced hepatitis C: The international telaprevir access program. J Hepatol. 2014;61(5):976-83.

325. Curry MP, Bacon B, Flamm SL, Kowdley KV, Dieterich D, Milligan S, et al. Effectiveness of 12 or 24 week ldv/sof and 12 week LDV/SOF + RBV in treatment-experienced patients with cirrhotic, genotype 1 hepatitis C: Real-world experience from the Trio network. Hepatology. 2015;62:755A.

326. Curry MP, Bacon B, Flamm SL, Tsai NCSC, Dieterich D, Milligan S, et al. Effectiveness of 8 or 12 week LDV/SOF in treatment-naïve patients with non-cirrhotic, genotype 1 Hepatitis C: Real-world experience from the TRIO Network. Hepatology. 2015;62:721A.

327. Dev AT, Mitchell J, Polkinghorne K, Skoien R, Stuart K, Cheng W, et al. Treatment safety and efficacy of Boceprevir-based triple therapy in genotype 1 hepatitis C: The Australian multicentre Boceprevir real world experience (SABRE-C). Hepatology. 2014;60:674A.

328. Fernandez C, Munoz de Rueda P, Alonso S, Prieto M, Martin-Alvarez A, Pons J, et al. Effectiveness of triple therapy with boceprevir or telaprevir in a multicentre clinical practice cohort of HCV treatment-experienced patients wtih advanced hepatitic fibrosis: SVR 12W after treatment. J Hepatol. 2014;60(1 Suppl):S488.

329. Fontaine H, Lacombe K, Dhiver C, Rosenthal E, Metivier S, Antonini-Michelle T, et al. LP23 : Daclatasvir plus sofosbuvir with or without ribavirin in patients with HIV–HCV co-infection: interim analysis of a French multicenter compassionate use program. J Hepatol. 2015;62, Supplement 2:S275.

330. Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016;64(6):1224-31.

331. Gill K, Fante G, Nafisi S, Moore A, Hepner A, Reynolds JA, et al. Sofosbuvir and ledipasvir for the treatment of HCV GT-1, cirrhotics and non-cirrhotics: Real-world effectiveness. Hepatology. 2015;62:757A.

332. Gray E, O'Leary A, C B, Norris S. Real-world effectiveness of DAA Regimens for HCV infection from an Irish national HCV registry. Pharmacoepidemiol Drug Saf. 2016;25(S3).

333. Ioannou GN, Beste LA, Green PK. Similar effectiveness of boceprevir and telaprevir treatment regimens for hepatitis C virus infection on the basis of a nationwide study of veterans. Clin Gastroenterol Hepatol. 2014;12(8):1371-80.

334. Khalid H, Khalid O, Hilton R, Bhatia R, Bhatti F, Bacon BR. Telaprevir: A real world experience. Gastroenterology. 2013;144(5):S980-S1.

335. Khalid O, Khalid H, Hilton R, Bhatia R, Bhatti F, Bacon BR. Boceprevir: A real world experience. Gastroenterology. 2013;144(5):S984.

336. Lai C, Witt DJ, M.A W. Real-world effectiveness of sofosbuvir (SOF), telaprevir and boceprevir (T, B) based in therapy for hepatitis C virus (HCV): An analysis in a large integrated health care system. J Hepatol. 2015;2015(1 Supp):S658.

337. Lebovics E, Maranino AN, Zahiruddin A, Gupta N, Frenkel J, Lebovics N, et al. Single-center real-world experience of sofosbuvir plus simeprevir for 12 weeks for genotype 1 chronic hepatitis C with advanced fibrosis. Gastroenterology. 2015;148(4):S1084.

338. Mauss S, Böker K, Buggisch P, Christensen S, Hofmann WP, Schott E, et al. Real-life experience with first generation HCV protease inhibitor therapy in Germany: The prospective, non-interventional PAN cohort. Z Gastroenterol. 2015;53(7):644-54.

339. Mauss S, Buti M, Ryder SD, Isakov V, Parana R, Kalsekar A, et al. SVR rates with telaprevir and boceprevir in us clinical practice. Gastroenterology. 2014;146(5):S-980.

340. Nazareth S, Fragomeli V, Colman A, Mason S, Morales B, Jones T, et al. The first Australasian experience with boceprevir: Treatment outcomes, adverse events and adherence. Hepatology International. 2014;8(1):S184.

341. Nguyen-Khac E, Pariente A, Lesgourgues B, Andre R, Bernard-Chabert B, Dao T, et al. Simeprevir plus sofosbuvir for the treatment of hepatitis C genotype 1 and 4 in a French mulitcenter cohort in real life: Real SimSof study. Hepatology. 2015;62(S1):735A-6A.

342. Petersen J, Olah K, Unger S, Lorenzen T, Kuhlendahl F, Wursthorn K, et al. Real world treatment with first generation triple therapy for HCV-GT1 difficult-to-treat patients: Final results of an observational study in patients with advanced liver disease and non-response. J Hepatol. 2014;60(1 Supp):S486.

343. Price JC, Murphy RC, Shvachko VA, Pauly MP, Manos MM. Effectiveness of Telaprevir and Boceprevir Triple Therapy for Patients with Hepatitis C Virus Infection in a Large Integrated Care Setting. Dig Dis Sci. 2014;59(12):3043-52.

344. Reddy R, Lim JK, Kuo A, Di Bisceglie AM, Vargas HE, Galati JS, et al. All oral HCV therapy is safe and effective in patients with decompensated cirrhosis: Interim report from the HCV-target real world experience. J Hepatol. 2015;62:S193.

345. Rodriguez EA, Levy C, Martin P, Bhamidimarri KR. Efficacy of sofosbuvir and simeprevir (COSMOS regimen) in hepatitis C genotype 1 in decompensated cirrhosis: A tertiary-center experience. Hepatology. 2015;62:806A-7A.

346. Roytman M, Tang A, Wu C, Piotrowski J, Hong L, Trujillo R, et al. Real life experience with Sofobuvir and Ledipasvir Fixed Dose Regimen in the Multicentric Cohort of Patients with Chronic Hepatitis C. Hepatology. 2015;62(S1):761A-2A.

347. Salmeron J, Vinaixa C, Berenguer R, Pascasio JM, Sanchez Ruano JJ, Serra MA, et al. Effectiveness and safety of first-generation protease inhibitors in clinical practice: Hepatitis C virus patients with advanced fibrosis. World J Gastroenterol. 2015;21(30):9163-74.

348. Sukeepaisarnjaroen W, Pham T, Tanwandee T, Nazareth S, Galhenage S, Mollison L, et al. Boceprevir early-access for advanced-fibrosis/cirrhosis in Asia-Pacific hepatitis C virus genotype 1 non-responders/relapsers. World J Gastroenterol. 2015;21(28):8660-9.

349. Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, et al. Effectiveness of Simeprevir Plus Sofosbuvir, With or Without Ribavirin, in Real-World Patients With HCV Genotype 1 Infection. Gastroenterology. 2016;150(2):419-29.

350. Terrault N, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. Treatment outcomes with 8, 12 and 24 week regimens of ledipasvir/sofosbuvir for the treatment of hepatitis C infection: Analysis of a multicenter prospective observational study. Hepatology. 2015;62:256A.

351. Vo KP, Vutien P, Akiyama MJ, Vu VD, Ha NB, Piotrowski JI, et al. Poor Sustained Virological Response in a Multicenter Real-Life Cohort of Chronic Hepatitis C Patients Treated with Pegylated Interferon and Ribavirin plus Telaprevir or Boceprevir. Dig Dis Sci. 2015;60(4):1045-51.

352. Walker DR, Pedrosa MC, Manthena SR, Patel N, Marx SE. Early View of the Effectiveness of New Direct-Acting Antiviral (DAA) Regimens in Patients with Hepatitis C Virus (HCV). Adv Ther. 2015.

353. Wehmeyer MH, Eissing F, Jordan S, Roder C, Hennigs A, Degen O, et al. Safety and efficacy of protease inhibitor based combination therapy in a single-center "real-life" cohort of 110 patients with chronic hepatitis C genotype 1 infection. BMC Gastroenterol. 2014;14:87.

354. Welzel T, Herzer K, Ferenci P, Petersen J, Gschwantler M, Cornberg M, et al. Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: Interim results of a compassionate use program. J Viral Hepat. 2015;22:4-5.

355. Werner CR, Franz C, Egetemeyr DP, Beck R, Malek NP, Lauer UM, et al. First-generation protease inhibitor-triple therapy: SVR 24, safety, and predictors of response in a large single center cohort. Virol J. 2015;12:37.

356. Thiagarajan P, Ryder SD. The hepatitis C revolution part 1: antiviral treatment options. Curr Opin Infect Dis. 2015;28(6):563-71.

357. Kwok M, Foster T, Steinberg M. Expedited Programs for Serious Conditions: An Update on Breakthrough Therapy Designation. Clin Ther. 2015;37(9):2104-20.

358. Sterling RK, Dharel N. Treatment of hepatitis C, then, now and tomorrow. Evid Based Med. 2015;20(1):23.

359. Lievre M, Cucherat M, Leizorovicz A. Pooling, meta-analysis, and the evaluation of drug safety. Curr Control Trials Cardiovasc Med. 2002;3(1):6.

360. Berry L, Irving W. Predictors of hepatitis C treatment response: what's new? Expert Rev Anti Infect Ther. 2014;12(2):183-91.

361. Gray E, O'Leary A, Stewart S, Bergin C, Cannon M, Courtney G, et al. High mortality during direct acting antiviral therapy for hepatitis C patients with Child's C cirrhosis: Results from the Irish Early Access Programme. J Hepatol. 2016;65(2):446-8.

362. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127-35.

363. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Comparative effectiveness of ledipasvir/sofosbuvir +/- ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin in 6961 genotype 1 patients treated in routine medical practice. Aliment Pharmacol Ther. 2016.

364. Younossi ZM, Park H, Gordon SC, Ferguson JR, Ahmed A, Dieterich D, et al. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C. Am J Manag Care. 2016;22(6 Spec No.):Sp205-11.

365. Gray E, O'Leary A, Kieran JA, Fogarty E, Dowling T, Norris S. Direct costs of interferon-based and interferon-free direct-acting antiviral regimens for the treatment of chronic hepatitis C infection. J Viral Hepat. 2016;23(9):677-86.

366. Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, de Joncheere K, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med. 2016;13(5):e1002032.

367. Smith-Palmer J, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. BMC Infect Dis. 2015;15:19.

368. Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. BMC Gastroenterol. 2013;13:16.

369. Basseri B, Yamini D, Chee G, Enayati PD, Tran T, Poordad F. Comorbidities associated with the increasing burden of hepatitis C infection. Liver international : official journal of the International Association for the Study of the Liver. 2010;30(7):1012-8.

370. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.

371. Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, et al. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651-60.

372. McEwan P, Ward T, Bennett H, Kalsekar A, Webster S, Brenner M, et al. Estimating the clinical and economic benefit associated with incremental improvements in sustained virologic response in chronic hepatitis C. PLoS One. 2015;10(1):e0117334.

373. Nevens F, Colle I, Michielsen P, Robaeys G, Moreno C, Caekelbergh K, et al. Resource use and cost of hepatitis C-related care. Eur J Gastroenterol Hepatol. 2012;24(10):1191-8.

374. Menzin J, White LA, Nichols C, Deniz B. The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective. BMC Health Serv Res. 2012;12:459.

375. Sethi N, Tapper EB, Vong A, Sethi S, Rourke M, Afdhal NH. Direct costs of first-generation protease inhibitors for the treatment of genotype 1 chronic hepatitis C viral infection. J Viral Hepat. 2015;22(12):974-6.

376. Bichoupan K, Martel-Laferriere V, Sachs D, Ng M, Schonfeld EA, Pappas A, et al. Costs of telaprevir-based triple therapy for hepatitis C: $189,000 per sustained virological response. Hepatology. 2014.

377. Manos MM, Darbinian J, Rubin J, Ray GT, Shvachko V, Denis B, et al. The effect of hepatitis C treatment response on medical costs: a longitudinal analysis in an integrated care setting. J Manag Care Pharm. 2013;19(6):438-47.

378. Tandon N, Balart LA, Laliberte F, Pilon D, Lefebvre P, Germain G, et al. Impact of completing chronic hepatitis C (CHC) treatment on post-therapy healthcare cost. J Med Econ. 2014;17(12):862-71.

379. Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. J Viral Hepat. 2014;21(3):208-15.

380. Ciani O, Jommi C. The role of health technology assessment bodies in shaping drug development. Drug Des Devel Ther. 2014;8:2273-81.

381. Guidelines for the Economic Evalutaion of Health Technologies in Ireland. Health Information and Quality Authority, 2010.http://www.hiqa.ie/publication/guidelines-economic-evaluation-health-techonologies-ireland.Report

382. Claxton K, Walker S, Palmer S, Schulpher M. Appropriate perspectives for health care decisions, CHE Research Paper. University of York, 2010.Report

383. Ready Reckoner 2013: Ready Reckoner of Acute Hospital Inpatient and Daycases Activity and Costs (Summarised by DRG) Relating to 2011 Costs and Activities. National Casemix Programme, 2013.http://www.casemix.ie.Report

384. Consolidated Salary Scales in Accordance With Financial Emergency Measures in the Public Interest Act 2013 2013 [cited 2014 30th July]. Available from: http://www.hse.ie/eng/staff/Benefits_Services/pay/July 2013.pdf

385. Central Expenditure Evaluation Unit: The Public Spending Code: Calculation of Staff Costs 2012 [cited 2014 30th July]. Available from: http://publicspendingcode.per.gov.ie/e-01-calculation-of-staff-costs/

386. PCRS Online Services: List of Reimbursable Items 2014 [cited 2014 30th July]. Available from: http://www.hse.ie/portal/eng/staff/PCRS/Online_Services/

387. Guidelines for the Inclusion of Drug Costs in Pharmacoeconomic Evalutions Version 1.10. National Centre for Pharmacoeconomics, 2012.Report

388. Central Statistics Office, Consumer Price Index [27th August 2014]. Available from: http://www.cso.ie/en/statistics/prices/consumerpriceindex/

389. Thorlund K, Druyts E, El Khoury AC, Mills EJ. Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. ClinicoEconomics and outcomes research : CEOR. 2012;4:349-59.

390. Pearlman BL, Traub N. Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More. Clin Infect Dis. 2011;52(7):889-900.

391. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology. 2009;49(3):729-38.

392. van der Meer AJ, Wedemeyer H, Feld JJ, Hansen BE, Manns MP, Zeuzem S, et al. Is there sufficient evidence to recommend antiviral therapy in hepatitis C? J Hepatol. 2014;60(1):191-6.

393. Koretz RL, Pleguezuelo M, Arvaniti V, Barrera Baena P, Ciria R, Gurusamy KS, et al. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. The Cochrane database of systematic reviews. 2013;1:Cd003617.

394. Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med. 2008;359(23):2429-41.

395. Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Delahooke TE, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58.

396. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-93.

397. Coverdale SA, Khan MH, Byth K, Lin R, Weltman M, George J, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol. 2004;99(4):636-44.

398. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52(3):833-44.

399. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006;10(21):1-113, iii.

400. NCPE. 2016. Personal Communication

401. O'Donohue F. Patient Registries in Ireland. Ireland: Medical Research Charities Group, 2012 28/2/12. Report No.http://www.mrcg.ie/assets/14/8514E0C8-0036-2920-9952158FCC3DF45D_document/MRCG_Report_2ndVersion__28.02.12.pdf.Report

402. Wells KJ, Holmes AK, Kohler SA, Rust CT, Rask KJ. Qualitative study of clinic staff members' experiences using an immunization registry. Arch Pediatr Adolesc Med. 2000;154(11):1118-22.

403. Christakis DA, Stewart L, Bibus D, Stout JW, Zerr DM, MacDonald JK, et al. Providers' perceptions of an immunization registry. Am J Prev Med. 1999;17(2):147-50.

404. Taha A, Ballou MM, Lama AE. Utilization of national patient registries by clinical nurse specialist: opportunities and implications. Clin Nurse Spec. 2014;28(1):56-62.

405. Graf A, Jones P, Cheng AC, Leder K. Healthcare provider knowledge, attitudes and practices in patients on the Victorian Spleen Registry. Aust N Z J Public Health. 2014;38(6):560-2.

406. Williams AM, Allingham RR, Beckwith HS, Liu PJ, Santiago-Turla C, Muir KW. Patient and family attitudes about an eye donation registry for research. Curr Eye Res. 2013;38(9):945-51.

407. Leahy J, Gray E, O'Leary A, Walsh C. Assessing the Impact of Incorporating Single Treatment Arm Evidence into a Network Meta Analysis. [Unpublished manuscript]. In press 2016

408. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ. 1998;316(7125):140-4.

409. Goring SM, Gustafson P, Liu Y, Saab S, Cline SK, Platt RW. Disconnected by design: analytic approach in treatment networks having no common comparator. Research synthesis methods. 2016.

410. Grayling MJ, Mander AP. Do single-arm trials have a role in drug development plans incorporating randomised trials? Pharm Stat. 2016;15(2):143-51.

411. Thom HH, Capkun G, Cerulli A, Nixon RM, Howard LS. Network meta-analysis combining individual patient and aggregate data from a mixture of study designs with an application to pulmonary arterial hypertension. BMC Med Res Methodol. 2015;15:34.

412. Kieran J. The Cost-Effectiveness of Hepatitis C Treatment in Ireland: A Multi-Technology Assessment. Dublin, Ireland: The University of Dublin, Trinity College; 2015.Thesis

413. van Dongen N, Nuijten M. PIP Data for Health Economic Modelling: An Alternative Data Source. ISPOR Connections. 2011;17(2).

414. Annemans L, Aristides M, Kubin M. Real-Life Data: A Growing Need. ISPOR Connections. 2007;13(6).

415. Berger ML. Can the pharmaceutical industry embrace comparative effectiveness research? A view from inside. Expert Rev Pharmacoecon Outcomes Res. 2013;13(5):565-8.

416. Faria R, Woods B, Griffin S, Palmer S, Sculpher M, Ryder SD. Prevention of progression to cirrhosis in hepatitis C with fibrosis: effectiveness and cost effectiveness

of sequential therapy with new direct-acting anti-virals. Aliment Pharmacol Ther. 2016;44(8):866-76.

417. NICE. Simeprevir in Combination with Peginterferon Alfa and Ribavirin for Treating Genotypes 1 and 4 Chronic Hepatitis C. London: NICE, 2015.Report

418. NICE. Sofosbuvir for Treating Chronic Hepatitis C. London: NICE, 2015.Report

419. NICE. Ombitasvir-Paritaprevir-Ritonavir with or Without Dasabuvir for Treating Chronic Hepatitis C Infection. London: NICE, 2015.Report

420. NICE. Daclatasvir for Treating Chronic Hepatitis C. Lonodn: NICE, 2015.Report

421. NICE. Ledipasvir-Sofosbuvir for Treating Chronic Hepatitis C. London: NICE, 2015.Report

422. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol. 2014;60(3):530-7.

423. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015;162(6):397-406.

424. Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux G-P, et al. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 95141). J Hepatol. 2014;61(1):7-14.

425. San Miguel R, Gimeno-Ballester V, Blazquez A, Mar J. Cost-effectiveness analysis of sofosbuvir-based regimens for chronic hepatitis C. Gut. 2015;64(8):1277-88.

426. Leleu H, Blachier M, Rosa I. Cost-effectiveness of sofosbuvir in the treatment of patients with hepatitis C. J Viral Hepat. 2015;22(4):376-83.

427. Bennett H, Gordon J, Jones B, Ward T, Webster S, Kalsekar A, et al. Hepatitis C disease transmission and treatment uptake: impact on the cost-effectiveness of new direct-acting antiviral therapies. The European journal of health economics : HEPAC : health economics in prevention and care. 2016.

428. Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J, et al. Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. J Hepatol. 2016;65(1):17-25.

429. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65(4):727-33.

430. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016;65(4):719-26.

431. ANRS. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016;65(4):734-40.

432. Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016;65(4):741-7.

433. Faria R, Hernandez Alava M, Manca A, Wailoo A. NICE DSU technical support document 17: the use of observational data to inform estimates of treatment effectiveness for technology appraisal: methods for comparative individual patient data. Sheffield: NICE Decision Support Unit. 2015.

434. Korn A. The Value of Observational Data in Health Care Decisions. Value and Outcomes Spotlight. 2015;March/April 2015.

435. Payne K, Pashos C, Schrammel P, Wilcox T. Making the 'MOST' of Prospective Observational Studies: Evidence Matters, United Biosource; [cited 2016 22nd July]. Available from: http://www.paramountcommunication.com/ubc/pdf/13_Prospective_Observational_Studies.pdf

436. Kieran J, Mushtaq H, Bergin C, Norris S, Barry M. Demographics and Health-State Utilities of Irish Patients With Hepatitis C Infection; Use of the 5-Level EQ-5D Questionnaire. Value Health. 2012;15(7):A528.

437. NCPE. National Hepatitis C Treatment Guidelines 2016. Personal Communication

438. Woods B, Faria R, Griffin S. Assessing the Value of New Treatments for Hepatitis C: Are International Decision Makers Getting this Right? Pharmacoeconomics. 2016;34(5):427-33.

439. Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? Gut. 2015;64(11):1800-9.

440. HSE. Special Delivery Unit: Unscheduled Care Strategic Plan. Dublin, Ireland: HSE, 2013.http://www.ntpf.ie/home/PDF/SDU UCSP Irish Logo.pdf

.Report

441. HSE. TrolleyGAR Reports Dublin, Ireland2013 [cited 2016 14th August]. Available from: http://www.nehb.ie/eng/about/Who/acute/trolleygar/

442. McCullagh LM, Adams R, Barry M, Schmitz S, Walsh C. Evaluation Of 'Real-World' Ipilimumab Data In Ireland. Value Health. 2015;18(7):A441.

443. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24.

444. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials. 2007;8:38.

445. Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: is it time? CMAJ. 2010;182(15):1638-42.