

A study of the clinical impact and outcomes of pharmacist-led interventions in the outpatient model of care for Hepatitis C patients in Ireland and their development into a novel complex intervention toolkit.

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Summary

Hepatitis C (HCV) is a major cause of morbidity and mortality worldwide. The availability of highly effective treatments has made the elimination of HCV a realistic goal. Simplified and devolved models of HCV care are needed to reach patients most in need of treatment. This research project focused on the clinical impact and outcome of pharmacist-led interventions in HCV patient care and how these interventions could be utilised to develop a novel complex intervention toolkit for use as part of devolved models of HCV patient care.

Phase one of this research project involved an assessment of the pharmacist-led processes of medication reconciliation and drug-drug interaction (DDI) identification and management. An analysis among 300 patients of pharmacist-led medication reconciliation, identified episodes of medication variances affecting 74% (N = 222) of patients. Further sub-analysis of fifty patient cases identified that 16.3% of medication variances identified during the medication reconciliation process were classified as severe and significant in terms of the potential for patient harm. This study's findings re-enforced that the process of pharmacist-led medication reconciliation is essential to identify an accurate patient medication list, so as to ensure the most appropriate HCV treatment is selected and all potential DDIs are identified and effectively managed. Review of pharmacist-led DDI assessment and management identified that 71% of the study population (N = 300) were at risk of a potential DDI with HCV therapy. This represents an average of 1.59 DDIs per patient. DDIs classified as potentially severe, affected 14% of the study population. A change in planned HCV treatment was required for eight patients due to severe unavoidable interactions with anti-epileptic medications and antiretroviral therapy. Sub-analysis of the epilepsy patient group, who were subject to severe potential DDIs found that they had a statistically significantly longer timeline to HCV treatment initiation when compared with matched controls (Log rank test $p = 0.006$, HR 5.652 (95% CI 1.428, 22.379)). The rate of acceptance of pharmacist-led DDI management plans was high overall, at 96.9%. Sustained virological response (SVR) 12 was achieved by 92.7% of

the study population. The findings of these research studies provided justification for inclusion of these pharmaceutical care activities as building blocks for complex intervention toolkit development in phase two of this research.

The pre-treatment patient assessment (PTPA) complex intervention toolkit design and development study created a functional tool guided by the positive evidence base identified for the pharmacist-led activities of medication reconciliation and DDI assessment in phase one. The development process guided by the Medical Research Council (MRC) framework, employed a stakeholder research group and conducted feasibility and optimisation studies to refine and develop the components of the toolkit, with the proposal of 29 new additions or changes to the toolkit, of which 26 were accepted. The pilot study then provided preliminary objective data on PTPA toolkit use and facilitated sample size calculation for the evaluation study. The findings of the evaluation study confirmed the effectiveness of the PTPA toolkit in aiding pharmacists and doctors in selecting the optimum HCV treatment for patients ($p < 0.05$) and in improving DDI detections rates among pharmacist, doctors and nurses ($P < 0.05$). It has, as evidenced in the studies undertaken to date, the potential to support the devolvement of DAA based therapy to secondary and primary care services. Evaluation study survey participants responded positively to the PTPA toolkit with 92% reporting that the toolkit would be a useful potential development in HCV care.

This study provides a novel approach to expanding the model of care, in the field of HCV treatment, and represents an important contribution to the limited data surrounding complex intervention development for use in the area of HCV patient care. The PTPA toolkit has the potential to be utilised to optimise HCV treatment selection for patients, as part of expanded cascade of HCV care.

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List of Abbreviations

ADE	Adverse drug event
AED	Anti-epileptic medication
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CAM	Complementary and alternative medicines
COPD	Chronic obstructive pulmonary disease
CPCP	Comprehensive pharmaceutical care programme
CTP	Child Pugh Score
CYP450	Cytochrome P450 isoenzymes
DAA	Direct-acting anti-viral
DCV	Daclatasvir
DBST	Dried blood spot testing
DDI	Drug-drug interaction
EASL	European Association for the Study of Liver Disease
ECHO	The Extension for Community Healthcare Outcomes
EFPIA	European Federation of Pharmaceutical Industries and Associations
EU	European Union
FIB-4	Fibrosis-4 Index for Liver Fibrosis
GDPR	General Data Protection Regulations
GP	General practitioners
G/P	Glecaprevir and pibrentasvir
GGT	Gamma-glutamyl transferase
GUIDe	Department of Genito Urinary and Infectious Diseases
HBV	Hepatitis B

HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HCV	Hepatitis C
HIQA	Health Information and Quality Authority
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICC	Intra-class correlation coefficient
IDU	Injecting drug use
IFN	Interferon
INR	International normalised ration
IRR	Inter-rater reliability
IPHA	Irish Pharmaceutical Healthcare Association
IRR	Inter-rater reliability
LDV	Ledipasvir
MAI	Medication Appropriateness Index
MDT	Multidisciplinary team
MELDNa	Model for end-stage liver disease
MOST	Multiphase optimisation strategy
MRCI	Medication Regimen Complexity Index
MSM	Men who have sex with men
MTM	Medication therapy management
MRC	Medical Research Council
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NSAIDs	Non-steroidal anti-inflammatory drugs
OATP	Organic anion transporting polypeptide
OGD	Oesophago-gastroduodenoscopy
OR	Odds ratio

OST	Opioid substitution therapy
OTC	Over the counter
P-gp	P-glycoprotein
PPI	Proton pump inhibitor
P/rOD	Paritaprevir (boosted with ritonavir), ombitasvir and dasabuvir
PTPA	Pre-treatment patient assessment
PWIDs	People who inject drugs
RBV	Ribavirin
RCT	Randomised control trial
REC	Research Ethics Committee
SOF	Sofosbuvir
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
SVR	Sustained virological response
TDM	Therapeutic drug monitoring
UGT	UDP-glucuronosyltransferase
UK	United Kingdom
US	United States of America
VA	Veterans Affairs
VAS	Visual Analogue Scale
VEL	Velpatasvir
VOX	Voxilaprevir
VTE	Venous thromboembolism
WHO	World Health Organisation

Chapter 1: Introduction

1.1. Hepatitis C: The virus, its incidence and prevalence

Hepatitis C (HCV), a virus from the Flaviviridae family was first identified in 1989(1). There are seven major HCV genotypes whose prevalence varies geographically (2). Genotypes 1 and 3 account for the majority of HCV infection worldwide (44% and 25%, respectively) (3). Genotype 1 accounts for the majority of infections in North America, South America, and Europe (2).

HCV is a major cause of liver disease morbidity and mortality worldwide with an estimated prevalence of 1% (95% CI 0.8 – 1.1%) (4). The World Health Organisation (WHO) estimated that in 2015, 399, 000 people died from cirrhosis or hepatocellular carcinoma (HCC) caused by HCV infection (4, 5). In Ireland, the overall prevalence of chronic HCV in adults is estimated to be between 0.4 and 0.8% (6). There were 589 notifications of HCV infection in 2018 (13/100,000 population) (7). The notification rate was significantly higher in the more populated and high density city areas in the eastern regions of the country (70% of cases) compared to the rest of Ireland.(8) Among the injecting drug use (IDU) population the prevalence of HCV antibodies is as high as 84% (9).

Data reported from the United States (US) reports that mortality from chronic HCV in that country has now surpassed mortality from more than 60 other nationally notifiable infectious diseases, including human immunodeficiency virus (HIV) infection and tuberculosis (10). HCV infection also continues to be a major public health problem in Europe, with a prevalence seven times greater than that of HIV (11). It is now estimated that there are 5.6 million people chronically infected in Europe.

1.2. Hepatitis C: The health implications

HCV infection causes chronic viral hepatitis. While the long-term natural history and impact of HCV infection is variable and remains incompletely defined, modelling studies forecast substantial increases in morbidity and mortality among persons with chronic HCV as they age into their third, fourth, and fifth decades (12, 13). Many co-factors have been identified which increase an individual's risk of developing significant fibrosis or cirrhosis (14). These include age at time of infection, male gender, alcohol consumption, obesity, insulin resistance, type 2 diabetes, co-infection with hepatitis B (HBV) or HIV, immunosuppressive medications and genetic factors (14). If chronic HCV infection goes undetected and untreated it may lead to cirrhosis, hepatic decompensation and HCC.

Development of hepatic fibrosis in the HCV seropositive population is clinically silent in the early stages of disease, and therefore identification of disease progression is challenging (15). It is estimated that 15-30% of patients chronically infected with HCV will progress to cirrhosis within 30 years of virus acquisition (2). Overall, once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation (14). Following an episode of decompensation, the risk of death in the following year is between 15% and 20% (14). HCV is one of the leading causes of end-stage liver disease, HCC and liver related deaths in the western world. It is also one of the main indications for liver transplantation worldwide (12). The HCV-related disease burden continues to increase as the infected patient population ages and advances to late stage liver disease (3).

It must also be noted that the negative health effects of chronic HCV infection extend beyond liver-related morbidity and can impact on the overall quality of life of patients (14). Chronic HCV infection is associated with multiple extrahepatic manifestations. These include thyroid dysfunction, skin disorders, cryoglobulinemias including vasculitis and glomerulonephritis and B-cell non-Hodgkin

lymphoma. Neurological manifestations of HCV infection include fatigue and cognitive impairment (16). HCV infected patients also have increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality. A large, prospective cohort study found that patients with chronic HCV infection, defined as having detectable HCV virus in serum, had an elevated risk of death from both hepatic and non-hepatic diseases. These included cardiovascular and renal diseases, compared with uninfected patients and those with antibodies to HCV (anti-HCV) but no detectable HCV virus in serum (17). HCV also greatly impacts quality of life for the families and communities of those with chronic HCV infection (11).

1.3. Healthcare burden of Hepatitis C infection

Given the significant impact of chronic HCV infection on patient morbidity and mortality, it is not surprising that it is associated with a significant healthcare resource burden and consequent budget impact.

A study by Kieran *et al* in the Irish healthcare setting identified that direct medical costs associated with HCV patient care are substantial and that with progression of liver disease the costs increase exponentially (18). The study identified that the annual mean costs of care for patients with untreated chronic HCV infection (excluding the cost of HCV treatment) ranged from €398 per patient with mild fibrosis to €1790 per patient with compensated cirrhosis and €137,176 for those in the first-year post liver transplantation. The cost of HCV infection to other health systems internationally are also known to be significant. A systematic review by Khoury *et al*, published in 2012, collated study data from Europe, the US and Asia assessing the median cost of untreated HCV infection associated with specific liver disease complications including refractory ascites (\$16,740), HCC (\$15,310), variceal bleeding (\$12,190) and hepatic encephalopathy (\$9180).(19) Costs to health systems include ongoing treatment of cirrhosis, HCC and end-stage renal disease, among others, which amount to a considerable expenditure by European countries on an annual basis (11).

In a survey encompassing five European countries, the estimated direct and indirect healthcare costs in caring for patients with chronic HCV were 76% and 65% higher, respectively, than people without HCV (20). This figure excludes the cost of HCV treatment itself. In the US, it was expected that HCV treatment-related costs will total \$8 billion annually on an on-going basis (21, 22).

HCV is also associated with a loss of productivity among those infected, with patients unable to fully participate in work activities and in society (11, 20). A survey conducted within the European Union (EU) in 2010, consisting of more than 57,000 respondents, reported that patients with HCV infection had more work impairment, a lower health-related quality of life and more annual physician visits than HCV negative patients (20).

A factor which adds to the increasing cost of caring for patients with chronic HCV in the majority of countries, is the increasing HCV-related liver disease burden as a result of an ageing population infected during peak HCV epidemics in the 1960's and 1970's, known as "baby boomers" (23). Given that the demand for healthcare relating to serious liver complications in HCV patients is expected to intensify significantly in the next decade, the impact on healthcare budgets will continue to grow (9). Previous research has proven that among patients with chronic HCV infection and advanced hepatic fibrosis, sustained virological response (SVR), achieved after successful HCV therapy, is associated with lower all-cause mortality and reduced healthcare expenditure (24). However, these highly effective new treatment options carry a significant budget impact. The average monetary cost to achieve SVR with an interferon (IFN)- free direct acting anti-virals (DAA) regimens in Ireland was estimated to be €81,873 per patient in 2016 (25). With the licensing of multiple DAA regimens now a reality, in addition to the implementation of national HCV treatment programmes in many countries, the cost of treatment has been reduced, however it still represents a significant cost burden to health services worldwide.

1.4. Hepatitis C: The treatment

Starting in the early 1990s, interferon-based therapy was the standard of care for HCV treatment internationally up until 2014. However, in the last six years HCV infection has been transformed with the development and licensing of highly effective IFN-free direct-acting anti-viral regimens. Oral DAA therapies now offer SVR rates greater than 95% in the majority of the patient population with minimal side effects.

1.4.1. Interferon and ribavirin

Prior to the availability of DAAs, IFN and ribavirin (RBV) were standard of care in the treatment of chronic HCV infection. Treatment with IFN and RBV-based therapies was continued for at least 24-48 weeks using response guided therapy rules. SVR rates for dual IFN/RBV therapy ranged from 40-50% for genotype 1 infection to more than 75% in patients with genotype 2 and 3 infection (26, 27). In some patient cohorts however, including patients co-infected with HIV, SVR rates were less than 20% (28). This meant a treatment failure rate of up to 80% in some patient cohorts. IFN and RBV treatment was associated with a multitude of side effects which often led to high treatment discontinuation rates and deterred many patients from initiating treatment at all. Common side effects included anaemia, chronic fatigue, alopecia, depression, anxiety, insomnia, thrombocytopenia, pancytopenia, thyroid dysfunction, skin rash, increased risk of infection due to neutropenia, headache, dizziness and constipation (29).

For multiple patient groups treatment with IFN and RBV was contraindicated, including patients with psychiatric diagnoses, decompensated liver cirrhosis, epilepsy, pregnancy, autoimmune hepatitis and HIV patients taking certain antiretroviral medications (30). The current burden of chronic HCV infection worldwide has been confounded by the suboptimal outcomes achieved with IFN-based treatment regimens.

Prior research has proven that among patients with chronic HCV infection and advanced hepatic fibrosis, SVR achieved after successful HCV therapy, is associated with lower all-cause mortality and reduced healthcare expenditure (24). Achievement of a SVR is associated with a reduction in portal hypertension, hepatic decompensation, HCC and liver related mortality in patients with compensated cirrhosis (14). Attaining SVR during the era of treatment with IFN and RBV therapy was challenging, with treatment failure or discontinuation a common occurrence (31-33).

1.4.2. Direct-acting antivirals

In 2011, the first HCV DAA, telaprevir was licensed for use with the second, boceprevir, licensed shortly after. When used in conjunction with IFN and RBV, the first approved protease inhibitors, telaprevir and boceprevir, increased the SVR rate for HCV genotype 1 infection to 60–70% (34, 35). However, it must be noted that this increase in SVR came at the cost of considerable side effects to the patient, due to telaprevir and boceprevir, including significant anaemia, potential for severe skin reactions, haemorrhoids, dysgeusia and gastrointestinal upset (36). These significant and severe adverse effects led to high discontinuation rates among patients treated with these regimens. For example in one study by Miallhes *et al* early discontinuation of treatment was reported in 9 out of 59 patients(15.3%) due to adverse effects (37).

In 2013, another protease inhibitor, simeprevir, was approved for use in genotype 1 infection (36). While simeprevir did not achieve much increase in SVR results (SVR = 80%) beyond telaprevir or boceprevir, it had a significantly reduced side effect profile (38). Resistance testing to identify the presence of the NS3 substitution Q80K was required for patients with genotype 1a being assessed for treatment with simeprevir. Presence of the mutation was considered a negative predictor for response to treatment (39). Response guided therapy and stopping rules were in place for telaprevir, boceprevir and simeprevir based on HCV viral load results at week 4 and week 12 of treatment.

Since the licensing of the first-generation HCV protease inhibitors, the pharmaceutical care of HCV has seen an intensity of anti-viral drug development not witnessed since the licensing of HIV anti-retroviral therapy in the 1990s (Figure 1.1). Sofosbuvir (SOF), a pan-genotypic NS5B polymerase inhibitor, was approved for use in 2013. When combined with IFN and RBV, SOF provided SVR rates of between 80- 89% after 12 weeks treatment (36). The subsequent availability of another class of DAA, NS5A inhibitors, including daclatasvir (DCV), ombitasvir and ledipasvir (LDV) made the idea of IFN-free therapy a reality.

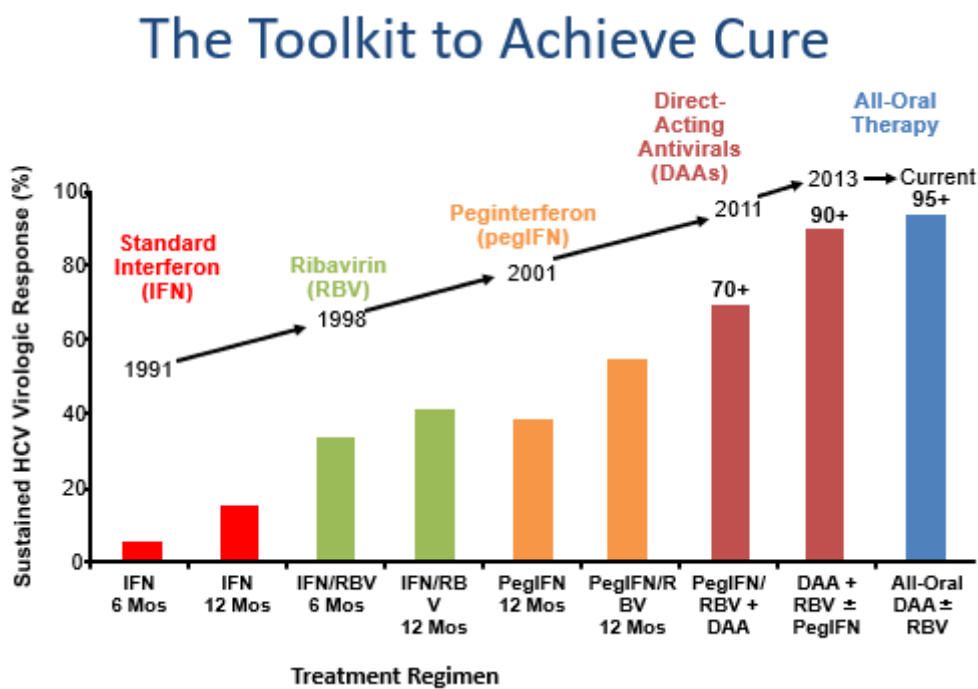


Figure 1.1 The toolkit to achieve cure: HCV treatment developments 1991-2019(27, 35, 40-46)

Numerous co-formulated DAA products have become available since then, providing patients with multiple DAA therapy options. The regimen of sofosbuvir/ledipasvir (SOF/LDV), licensed in 2014 provided a one pill per day treatment regimen for patients with genotype 1 or 4 infection. SVR rates of 97-99% were reported in clinical trials for this regimen in treatment naive non-cirrhotic and compensated cirrhosis patients with genotype 1 infection (45). While disparate SVR rates were

reported in the era of IFN/RBV therapy trial outcomes, SVR rates among patients with HIV co-infection were comparable to the HCV mono-infection cohort (47).

The triple DAA regimen of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (P/rOD) with co-prescribed RBV was licensed in 2015 and achieved SVR rates >95% in non-cirrhotic patients with HCV genotype 1a and 1b infection (43). High SVR rates were also obtained in patients with compensated cirrhosis treated for 12 to 24 weeks (SVR = 91.8% - 95.9%) (48). Trial data has been supported by publications from large real-world cohorts which report similarly high SVR rates (49). This regimen is suitable for use in all stages of renal impairment including in patients receiving dialysis with comparable SVR rates obtained (50). As further DAA regimens were licensed, P/rOD was withdrawn from first line use due to pill burden (4 tablets per day) and a twice daily dosing regimen. In addition, unlike P/rOD, other regimens do not require ribavirin which significantly reduces the risk of adverse effects for patients.

The regimen of SOF and DCV was the first pan-genotypic DAA regimen to be licensed. Data from a large real world French cohort identified high SVR rates, ranging from 92% (12-week SOF/DCV) to 99% (24-week SOF/DCV/RBV) (51). Among genotype 3 patients, SVR12 rates after 12 weeks treatment were 90% and 86% in treatment-naïve and treatment-experienced non-cirrhotic patients, respectively (52). SVR12 rates were higher in patients without cirrhosis (96%) than in those with cirrhosis (63%) (52).

The regimen of elbasvir/grazoprevir which was licensed for use in 2016 in genotypes 1, 4 and 6 infection represented the first DAA regimen without a NS5B polymerase inhibitor. Clinical trial data identified high SVR rates among patients with and without cirrhosis (90-100%) (42). An added benefit of this regimen was its safety and equivalent efficacy in patients with chronic kidney disease including patients on dialysis (53).

The regimen of sofosbuvir/velpatasvir (SOF/VEL) represented the first single tablet pan-genotypic DAA regimen and was licensed in 2017. Trial data in patients with genotypes 1, 2, 4, 5 and 6 reported SVR rates of 99% after 12 weeks of therapy for non-cirrhotic and compensated cirrhosis patients (41). These outcomes are mirrored in widely published real world datasets including studies from Germany and Spain (54, 55). As highlighted by data from a Spanish study by Esteban *et al*, genotype 3 patients with compensated cirrhosis benefit from the addition of RBV to the regimen of SOF/VEL. (SVR rate = 91% after 12 weeks SOF/VEL vs 96% after 12 weeks SOF/VEL/RBV) (55). A benefit of the regimens of SOF/LDV and SOF/VEL is their suitability and safety of use in patients with decompensated cirrhosis (56).

A second pangenotypic regimen, this time consisting of an HCV protease inhibitor and a NS5A inhibitor, glecaprevir and pibrentasvir (G/P), was licensed in 2017. Among non-cirrhotic patients this regimen offered a shortened therapy duration of 8 weeks while maintaining high SVR rates (99.1% in genotype 1) (57). SVR rates achieved among patients with compensated cirrhosis and genotype 1, 2, 4, 5 or 6 infection reached 99% and 95% among genotype 3 patients (58). The regimen of G/P is also the only pangenotypic regimen licensed for use in patients with chronic kidney disease, including patients receiving dialysis, producing equivalent SVR rates to other patient groups (SVR rate = 98) (59).

The last DAA licensed for use in 2017 was voxilaprevir (VOX) which is co-formulated with SOF/VEL as a single tablet formulation. While its product license indicates the potential for use of this regimen as a first line therapy, international treatment guidelines advise retaining this triple DAA regimen as a salvage therapy for re-treatment post DAA failure (60-64). A study of greater than 100 patients whom had previously been treated with a DAA-containing regimen, reported an SVR 12 rate of 95% post treatment (SVR rate = 89% in those with cirrhosis) with 12 weeks SOF/VEL/VOX (64).

Adverse effects are similar across the spectrum of IFN- free DAA regimens. The most commonly reported side effects of DAAs include headache, fatigue, mild skin rash, gastrointestinal upset and dizziness (41-43, 45, 57, 63, 65).

The potential combination of multiple different DAA agents in IFN-free regimens provides the opportunity to achieve high SVR rates with shortened treatment durations and a significantly reduced side effect profile. Pill burden is also significantly reduced from a high of 18 tablets per day (regimen of IFN/RBV/boceprevir) to the availability of single tablet co-formulations of SOF/LDV, SOF/VEL +/- VOX and elbasvir/grazoprevir.

Three classes of direct acting anti-viral agents (DAAs), now provide multiple drug regimen choices for prescribers, with associated SVR rates greater than 90% in the Irish DAA treatment cohort to date (66). There are currently nine DAAs licensed in the European Union for treatment of HCV infection (Table 1.1).

A large prospective cohort study undertaken in France identified that after adjustment for patient and virus specific variables, exposure to DAAs was associated with a decrease in all-cause mortality (adjusted hazard ratio (HR) 0.48, 95% CI 0.33-0.70) and HCC (adjusted HR 0.66, 0.46-0.93), and was not associated with decompensated cirrhosis (adjusted HR 1.14, 0.57-2.27) (67).

Given the high rates of SVR and good tolerability of new DAA regimens, international guidelines now recommend that all HCV-infected patients be considered for access to DAA therapy (13, 61, 66, 68, 69).

Table 1.1 Direct acting antivirals licensed for use in the European Union

Protease Inhibitors	NS5A inhibitors	NS5B polymerase inhibitors
Glecaprevir	Daclatasvir	Sofosbuvir
Grazoprevir	Elbasvir	
Voxilaprevir	Ledipasvir	
	Pibrentasvir	
	Velpatasvir	

Hepatitis C is the first major chronic viral illness that has become curable using anti-virals (36). The development of effective, well-tolerated, once-daily and short duration DAA therapy for the treatment of HCV infection has been revolutionary and provides an opportunity to stem the rising liver disease burden (70). With durations of therapy as short as 8 weeks, few side-effects and the fact that more than 90% of patients can be cured, treatment has become a realistic option for all people living with HCV infection internationally (71).

The new treatments have also broadened the population of patients suitable for treatment, in both number and complexity. Those previously unsuitable for treatment due to reasons of liver cirrhosis or contra-indicated co-morbidities now represent a large proportion of the patient population with the greatest treatment need.

Even with multiple treatment options available for HCV infection, the issue of HCV re-infection must also be considered given that the WHO aim is to achieve HCV eradication. In a study published by Islam *et al*, which looked at data from 1990 – 2013 (the pre- DAA era) there was a reinfection rate of 1.27/100 person-years of follow-up (72). Data from the same healthcare setting in British Columbia was also analysed for years where DAA treatments were available. Rossi *et al* reviewed treatment outcome and follow up in a cohort of 4,114 patients and identified an overall reinfection rates of 1.44 per 100 person years of follow-up (73). A significant number of re-infections occur among PWID and the MSM population. HCV models of care must encourage and make available regular opportunities for testing among these patient cohorts (72, 73).

DAA treatment failure, while uncommon (<5% of cases) does occur. In this patient group it is key that resistance testing is undertaken to determine if patients have developed any resistance mutations which may impair the antiviral activity of DAAs which may be used as part of a retreatment strategy (74). The importance of patient education around DAA regimen compliance and course completion cannot be understated. Research to date tells us that once NS5A and NS5B mutations emerge, they persist long term (75). This means that for patients who are poorly or non-compliant with multiple DAA regimens, development of resistance mutations may lead to an exhaustion of DAA retreatment options.

1.5. National Hepatitis C Programmes

The availability of highly effective treatments has made the global elimination of viral hepatitis a realistic goal (76). In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030, and the WHO introduced global targets for the care and management of HCV including “a 90% reduction in new cases of chronic HCV infection, a 65% reduction in HCV-related deaths, and treatment of 80% of eligible people with chronic HCV infections” (3, 76). The WHO estimated that implementing its strategy would cost US \$11.9 billion for the period 2016–21 (71).

Many countries have developed national HCV treatment programmes to get on track with WHO elimination targets. Some countries have committed to and invested heavily in HCV treatment programmes which is evidenced in their outcomes to date. However, the majority of countries are lagging behind and are not on target to eliminate hepatitis infection by 2030.

1.5.1. Screening & Diagnoses

Screening and diagnosing new patients are important factors in achieving WHO elimination targets. The undetected spread of HCV is one of the most important challenges to address in the HCV care

continuum, as the disease is often only detected in the late stages, if at all (11). The acute stage of HCV infection is usually asymptomatic, but approximately 75% of those infected develop chronic infection, which can cause cirrhosis of the liver, HCC and liver failure (8, 14). HCV patients often have no symptoms for the first 20-30 years of infection and therefore it is not uncommon for patients to remain undiagnosed until they present with the complications of end stage liver disease (11, 14). Research has highlighted that fewer than 40% of all cases are detected, even in high-income countries (11).

Since the onset of treatment with all oral DAA regimens some countries with high treatment rates (e.g. Australia) are now reporting a drop in treatment rates thought to be mainly due to those already diagnosed completing treatment (77). It is clear that some countries are simply not screening sufficient numbers of patients to maintain their treatment rates. As per Polaris data, the two exceptions are Egypt, which screened 4.5 million individuals in 2017 and Mongolia, where everyone aged 41-65 was screened for HCV in 2016 and those aged 18-40 were screened in 2017 (77). National screening campaigns are needed to identify patients infected with HCV. In Ireland, national HCV screening guidelines were launched in July 2017 (78).

1.5.2. National Treatment Strategies

Currently, 12 countries are on track to meet the WHO elimination targets that 194 countries globally signed up to in 2016 including Italy, Mongolia and Georgia (77). In all cases, these countries are treating at least 7% of their infected population each year, and have opened treatment up to all those infected (77). Globally, the total number of treated HCV patients increased from 1.8 million to 2.1 million between 2016 and 2017 but most of that growth occurred in middle income countries. In high income countries, the number of treated patients actually decreased (77).

This reduction in numbers treated may be due to multiple factors including a failure to upscale HCV screening and patient identification. Large numbers of patients with known HCV infection may have been linked with care but a significant number may remain undiagnosed due to lack of awareness around HCV infection risk and or lack of access to testing. As of 2015, it has been estimated that there are 290 million individuals worldwide who remain undiagnosed. Another factor to consider is that even in high income countries access to healthcare can be limited for some patient cohorts. For example, in the United States many patients are presented with barriers to HCV treatment access due to the wide variability in HCV treatment coverage by healthcare insurance providers (79, 80). Another important factor may be the price paid by countries for DAAs. Voluntary licensing schemes which offer DAAs to lower- and middle- income countries at lower prices which are not available to upper-middle and high-income countries. This coupled with poor health system funding or lack of commitment to HCV eradication at a national level may limit the numbers of patients able to avail of treatment (76).

Australia

DAA treatment was initiated for 32,600 people in 2016 with a further 21,370 treated in 2017. This now means that 14% of Australians known to have chronic HCV infection have initiated treatment. (70) (81, 82) . These high treatment numbers linked with an already high diagnosed proportion (estimated at 81%), and established harm reduction strategies provide the foundation for HCV elimination in Australia to be a realistic target (70).

Using a mathematical model incorporating DAA treatment, Kwon *et al* determined that Australia can meet the 80% reduction in HCV incidence by 2026, and 80% of eligible patients treated by 2028 through a feasible “intermediate” HCV treatment scenario (70). Additional strategies will be required however, including HCC screening and improved management of advanced liver disease complications, to substantially reduce liver-related mortality attributable to HCV infection (70).

Europe

HCV infection is a major public health problem in the European Union (EU). There is still a general lack of co-ordination among EU member states (11). Coordination must happen at the EU and national levels (11). Key points identified as part of the EU programme include access to affordable or free treatment and care, scale-up of harm reduction measures, improved links with marginalised patient groups and community and peer advocate engagement (11).

HCV treatment rates vary dramatically across the EU (ranging from 0.6% to 10.2%) and unfortunately in many countries there is a great discordance between prevalence rates and treatment rates (11). It is estimated that 21 European countries account for 80% of the burden of viraemic HCV infections but only a small number of countries (28%) are actively treating large numbers of patients (80% of the treated patients) (11). In Europe in 2015, approximately 130,000 patients (3.7% of patients) were treated. This represented a significant increase from previous years with IFN/RBV therapies (60,000-80,000/year) (11). It is feasible to achieve HCV elimination in the EU but this will require an increase in treatment numbers of 6%-10% per year, implementation of harm reduction strategies to reduce the rate of new infections and expanded screening and treatment access for all HCV-infected individuals (11).

Scotland

Scotland's Hepatitis C Action Plan, first published in 2006, has led to substantial progress in its HCV elimination strategy (83). The plan has led to a significant reduction in incident infection rates and has led to an increase in the proportion of people diagnosed, numbers initiating treatment and a reduction in the overall prevalence of infection (11). The initial plan was further expanded upon in 2018 when an updated plan entitled, "Eliminating Hepatitis C in Scotland: A Call to Action" was published. Since the inception of this plan in 2006 there has been an estimated 45% reduction in the number of people living with chronic HCV in Scotland from 38,000 to 21,000 (84). The

implications of this successful upscaling of treatment are already being felt by healthcare services with a 67% reduction in the number of new presentation liver decompensations between 2013 and 2018 with HCV-related deaths declining by 49% over this same time period (84).

In 2019, the Scottish government launched a HCV national elimination strategy (84). The aim of this plan, to achieve elimination of HCV sets treatment targets for the Scottish healthcare service, with an aim to treat at least 2,500 patients for HCV infection in 2019-2020 and to increase to at least 3,000 treatments annually from 2020-2021. The Scottish model now represents the gold standard in terms of HCV screening, diagnosis and treatment (84).

England

Between 2008 and 2014, it is estimated that approximately 5,100 patients were initiated on HCV treatment in England per year (85). With the availability of DAA therapy this number increased to just over 24,000 people between 2015 and 2018 (85). By the end of 2018 approximately 40,000 patients had been treated for HCV infection with an SVR rate of 95.1% (85). However, it is estimated that more than two thirds of the estimated 160, 000 people infected with HCV in England are still undiagnosed with a significant proportion of these patients coming from marginalised patient groups including PWIDs and homeless persons (86).

The healthcare service in England have implemented strategies to target high risk populations. Opt-out bloodborne virus testing is now fully implemented across the prison system in England (85). Research projects have assessed the impact of specific interventions to increase uptake of treatment among PWIDs (87). These interventions include the HepCATT study which assessed the impact of providing a facilitator, experienced in the area of HCV patient care, to addiction service clinics. The facilitators role was to provide training and education, to interact with patients, to streamline clinic practices with regard to HCV treatment and to introduce practices which would

encourage testing and treatment (e.g. dried blood spot testing (DBST)) (87). The findings of the feasibility study by Harrison *et al* identified strong evidence that engagement with HCV therapy was improved by the presence of a facilitator in the clinic setting (87).

In 2019, the National Health Service in England agreed an updated treatment strategy which will see them working in partnership with specific drug companies to proactively identify and treat patients with HCV infection. This multiannual plan will target case finding strategies to target the most at risk patient groups (86).

Germany

The German Action Plan on Hepatitis, developed in 2013, includes recommendations for improved patient education, provision of needle exchange services, an expanded model of care and increased staff training and education (11). The plan was informed by research including the DRUCK study (88). Research by this study group identified that HCV was endemic among the PWID populations in German cities with rates of HCV infection ranging from 42.3% and 75% (11, 88). All patients with chronic HCV infection are eligible for DAA treatment, regardless of liver fibrosis stage (89). Current engagement in opioid substitution therapy (OST) programmes ranges from 30.8% to 66.2% (88). Given that a significant proportion of patients with HCV infection are not engaged with OST services, devolvement of HCV treatment services must include multiple community settings, such as general practitioners (GPs) and homeless services, and not just addiction services. In addition, there is currently no HCV screening policy in place in Germany (89). To achieve HCV eradication, it is essential that such a policy is developed and implemented.

Portugal

The National Action Plan for HCV in Portugal is an example of a collaborative effort between the general public, healthcare researchers, clinicians, patients and healthcare staff. The plan outlines

new prevention policies and access models for HCV treatment along with the development of a national patient registry (11). In 2018, the model of care was expanded to capture the prison population. Specialist hospital-based staff began in-reach services into prisons to test and treat patients for HCV infection. To date the action plan has been associated with a 73% reduction in the incidence of HCC, a 92.5% reduction in the need for liver transplantation due to HCV infection and a 93.2% reduction in development of cirrhosis (11).

The Netherlands

HCV policies in the Netherlands have demonstrated the effectiveness of harm reduction strategies towards PWIDs (11). A study by Van den Berg *et al* identified that participation in a harm reduction programme which included OST and needle exchange was associated with a lower risk of HCV infection (90). HCV prevalence among another at risk group, HIV-positive men who have sex with men (MSMs), was found to have increased from 5.6% in 1995 to a peak of 20.9% in 2008 (91). Current policy regarding DAA treatment in the Netherlands is to target micro-elimination strategies at particular at-risk groups including PWIDs, MSMs, persons with haemophilia and homeless persons (92). Unrestricted access to DAA treatment for HCV infection has been available in the Netherlands since 2015. Since then there has been a 51% reduction in HCV infection among the MSM population (one of the micro-elimination cohorts) (93).

Ireland

HCV treatment strategies in Ireland are guided and co-ordinated by the National HCV Treatment Programme as part of the Health Service Executive and in conjunction with the Department of Health. The number of patients treated nationally up to the end of April 2019 with all IFN free DAA regimens was 4,227 patients. Current policy in Ireland is to provide treatment to all patients with chronic HCV infection regardless of fibrosis staging. Treatment is available to patients at hospital-based outpatient departments and community-based drug treatment clinics. Devolvement of

treatment to community-based GPs and pharmacies is currently in its pilot phase. National clinical guidelines for HCV screening were published in July 2017 (78). It is estimated that 60% of those with HCV infection in Ireland are undiagnosed (78). The Health Information and Quality Authority (HIQA) of Ireland are also currently undertaking a health technology assessment to investigate if birth cohort screening in Ireland would be cost effective. This birth cohort screening would offer testing for the hepatitis C virus to people in Ireland born between 1965 and 1985.

1.6. Expanding the Model of Care for Hepatitis C infection

The discovery and now widespread availability of, DAAs, has for the first time made elimination of HCV infection, at the population level, a possibility (11). The impact of DAAs on the HCV epidemic hinges on multiple steps from diagnosis, to referral to healthcare service, to patient evaluation, and finally treatment (94). HCV infection presents specific challenges that requires having diversity in the available models of HCV care, regardless of who prescribes the DAA therapy (23).

1.6.1. Barriers to accessing Hepatitis C treatment

Since initial DAA access with telaprevir and boceprevir in 2012, to current day DAA regimens, of which we have significant real-world experience, the landscape of HCV treatment has evolved from a specialist-driven model with few patients qualifying for treatment to an opportunity for non-specialists and other healthcare professionals (HCPs) to provide curative therapies to most patients (95). However, prescribing of DAAs still predominantly occurs in specialty services rather than general medical settings internationally(96). Although DAA regimens have driven up demand for HCV treatment, a mere fraction of HCV-infected individuals are offered treatment within specialty settings (97).

Currently in Ireland, the knowledge base around use of DAAs to treat HCV infection is confined to specialist centres and a limited number of addiction service prescribers. The skill mix and

experiences, even within these centres, are varied. Beyond specialist centres and drug treatment services there are no prescribers or other healthcare team members with experience of treating patients for HCV with DAAs. This centralised treatment model limits the reach of the National HCV Treatment Programme in Ireland in terms of patient identification, linkage to care and treatment, particularly among more marginalised patient groups. However, this is not unique to the Irish setting.

Another potential barrier to accessing DAA treatment across all treatment settings internationally is a lack of awareness of HCV status, given the asymptomatic nature of chronic HCV infection (Figure 1.2). Indeed, across the EU, it is estimated that as little as 36% of those living with chronic HCV infection have been diagnosed, and just 5% have been treated (23). In the US, a 2014 meta-analysis, identified that 50% of patients with HCV infection have been diagnosed with only 16% of patients having received treatment (98). HCV testing, diagnosis, patient linkage to care, and treatment uptake rates all need to be improved if WHO elimination targets are to be achieved (23).

Even with reasonable capacity in the specialty setting, travel to specialty clinics or even the idea of attending appointments in unfamiliar settings with unfamiliar healthcare providers can be a barrier for some marginalised populations disproportionately impacted by HCV infection (Figure 1.1) (97). A UK based study by Simpson *et al* identified that distance to a treatment site is a factor in HCV treatment uptake (99). The study found evidence that 'treated' individuals lived closer to HCV treatment services, compared to those who were lost to follow up before treatment initiation or confirmation of infection had been obtained (99). Living within 4 kilometres of a treatment facility was a strong predictor of having started treatment (99). This simple analysis has important implications for the strategic development of HCV services and highlights that bringing treatment opportunities out to patients in the community will help to increase testing and treatment uptake.

Other common themes and barriers identified around current low treatment uptake rates include the disjointed and multi-provider nature of HCV patient care, patient fear of treatment due to known side effects associated with IFN/RBV therapy, and issues related to social marginalisation and stigma experienced by PWIDs, homeless persons and other hard to reach populations (Figure 1.2). For many patients, even if they are aware of their diagnosis, complex healthcare needs and social issues mean that HCV treatment is not their priority. In addition, despite the clear pharmacoeconomic benefits of treating HCV infection, the cost of HCV treatment is still an obstacle in some countries where patients must assume some or all of the treatment costs. For example, Medicaid programmes in several US states have restricted access to DAAs based on the presence of advanced fibrosis (100). So, how can we improve treatment rates towards HCV elimination targets?

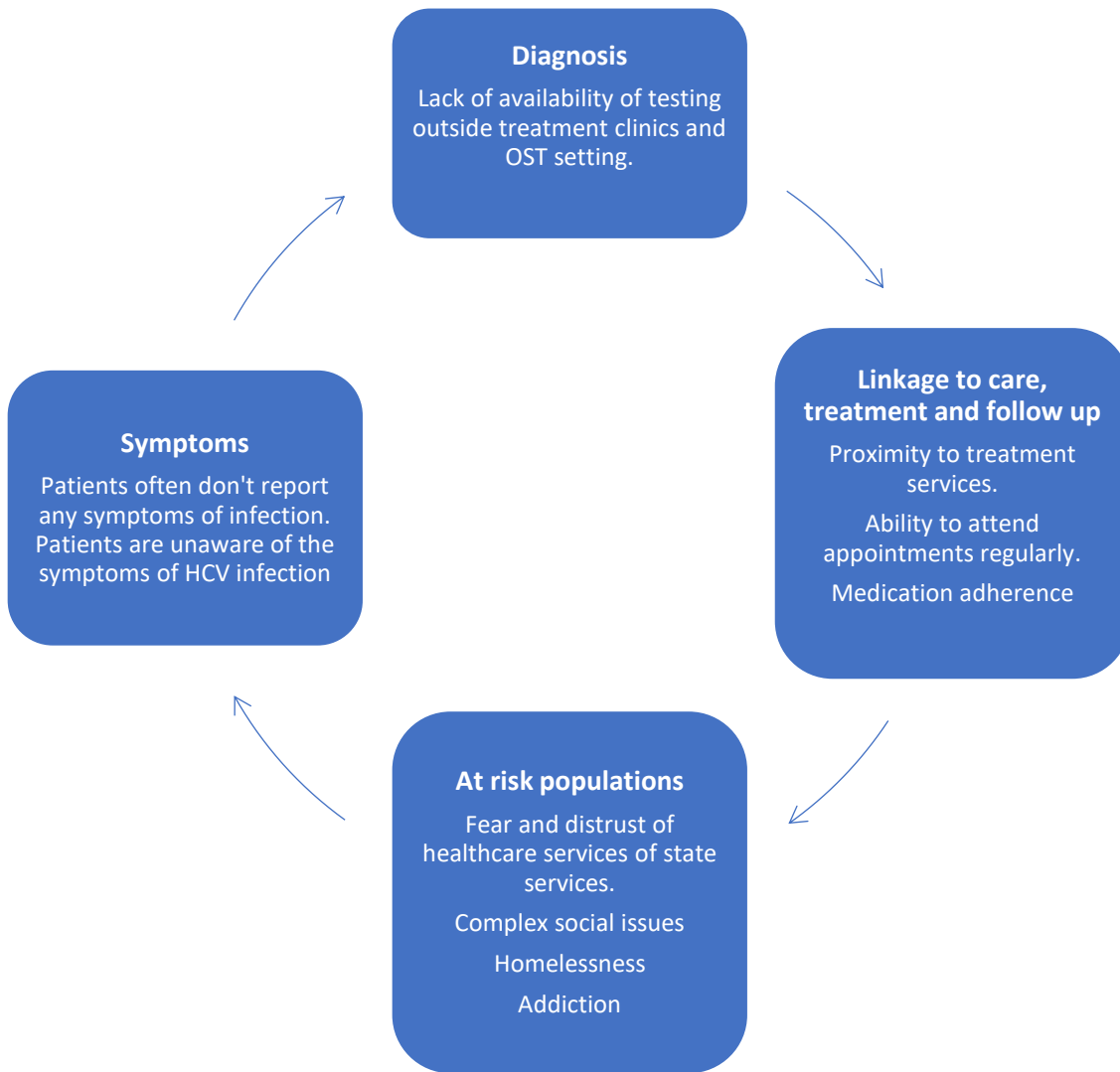


Figure 1.2 Barriers to HCV care engagement (94, 97, 99-101)

1.6.2. Strategies to improve access to Hepatitis C treatment

Strengthen linkage from testing to treatment

Patient identification is one of the biggest barriers remaining in the HCV cascade of care (94). The delivery of HCV testing and treatment through community-based care pathways has been shown to be feasible and DBST has been demonstrated to increase the uptake of testing from high-risk populations (102, 103) (104). However, systematic screening policies are lacking, and it is not clear which are the most cost-effective methods for recruiting patients into testing, care and treatment

programmes (11). Outcomes of a HCV clinical programme should be defined by successes in screening, diagnosis and linkage to care in addition to the number of patients successfully cured (95). Achieving WHO targets in terms of identifying HCV prevalence and incidence will require sustained HCV testing and linkage to care (70).

Devolution of care strategies to overcome patient-related barriers to HCV treatment

Scale up and devolution of DAA treatment is essential in achieving HCV treatment targets, but this constitutes an immense public health challenge (105). Showing that physicians in primary care settings can deliver HCV infection care is important in expanding treatment, and healthcare models doing so in the era of newer oral HCV medications are needed (106). Primary care healthcare teams are well-positioned to screen, assess and treat HCV infection in an outpatient setting while co-managing patients' other acute and chronic illnesses (107). To provide these non-specialists with the right tools to enable them to successfully engage in identifying and treating patients with HCV infection, we require innovative practice models (95).

Two systematic reviews have assessed the impact of evidence-based interventions along the HCV care continuum (108, 109). Interventions assessed included initiation of multidisciplinary team (MDT) meetings at HCV treatment clinics and co-location of mental health and hepatology outpatient services (110, 111). Both reviews found wide variances in research methods among the studies identified, with small sample sizes and a lack of control groups cited as reasons to view results with caution. However, study findings point to evidence-based interventions in HCV care being both clinically and cost effective (108).

Co-location of HCV treatment with other healthcare services

It is clear that models of care must adapt to address the needs of specific high-risk patient subgroups (e.g. PWID, homeless patients, patients with significant psychiatry co-morbidities) in the overall expanded model of care. Only by providing equitable scale up of DAA treatment to all patients with chronic HCV will real and sustained reductions in HCV incidence and prevalence be achieved (112). A systematic review by Zhou *et al* identified the importance of integrated approaches to HCV care, particularly for more vulnerable patient groups (e.g. IDU and homeless patients) who make up a large proportion of the patients who need to be treated most (108).

Primary care providers, have indicated a willingness to take on the task of HCV treatment with the support of experienced specialist providers and clinic teams (97). Currently in the EU, almost all countries require a specialist to prescribe and manage DAA therapy (23). Even in countries and jurisdictions where addiction specialists and primary care providers can prescribe DAAs, restrictions are in place via national treatment programmes (23).

Co-locating HCV treatment in settings in which patients are already engaged in care (such as primary care clinics, substance abuse treatment centres, and OST clinics) can overcome access barriers for patients unwilling or unable to seek specialty care (95). Care co-ordination has been found to reduce barriers to care and improve patient outcomes, particularly for hard-to-engage and hard-to-treat populations (113). Research of these multi-layered models of care for HCV management have shown the benefits and possibilities for increased screening, linkage to care and treatment initiation (114). The INSPIRE study, undertaken in the US, used an innovative care co-ordination model, which included integrated HCV clinical care to improve HCV outcomes and overall health and well-being (113). The study results demonstrated that the care co-ordination intervention was associated with a significantly higher probability of HCV treatment initiation and SVR when compared with a demographically similar cohort of HCV-positive patients (113).

Australian research has confirmed that patients with substance misuse and addiction issues had better outcomes when receiving care in a clinic with embedded support services (115). If proximity to treatment services is also a driver of loss to follow-up, such service co-location could significantly reduce this problem (99). Delivery of HCV treatment by community-based GPs, homeless service healthcare clinics and addiction services could greatly increase proximity of patients to treatment services. However, regardless of proximity of treatment services, there is a subset of patients at risk of HCV infection who will not engage with traditional healthcare services. Research is required to identify pathways to engage this population group in awareness campaigns, HCV testing and linkage to care.

Social inclusion care model and mental health supports

HCV disproportionately affects socio-economically disadvantaged persons including PWIDs, prisoners, migrants and the homeless (11). Some patients may fall within more than one of these groupings which may worsen their social isolation. For example, research completed in Dublin by Ni Cheallaigh *et al*, identified that homelessness was strongly associated with drug use with over 50% of homeless individuals reporting IDU (101).

Strategies to assist patients with complex needs have been described by Sublette *et al*, including patient advocacy (i.e. housing and income stability during treatment), practical problem solving to help patients adhere to treatment, ongoing patient feedback to provide positive reinforcement, and support to assess the psychological impact of treatment (116). Lasser *et al* reported the benefit of the inclusion of a social worker as part of the Safety Net HCV patient care team in a Boston clinic (106). The social worker helped patients to address any social issues linked to their health, to help patients better navigate healthcare services and also to facilitate engagement in HCV treatment (106). It is also important to recognise that patients infected with HCV often have psychological barriers to treatment initiation and completion and may require additional support (117). Some

models incorporate mental health professionals into their healthcare teams, resulting in higher HCV treatment completion rates (118).

Patients in addiction

PWIDs are a particularly vulnerable group who are at the highest risk of HCV infection. In Ireland and the majority of other countries worldwide, IDU is the most commonly reported risk factor for chronic HCV infection. Among PWIDs, the HCV seroprevalence is 60–84% globally (119). Poor linkage to and retention in healthcare services present a major barrier to HCV treatment among PWIDs (120). HCV cannot be eliminated without a concerted focus on raising awareness and co-ordinating prevention, testing, care and treatment among this population (11).

Key strands within the WHO strategy for HCV elimination include community engagement and peer support to address stigma and discrimination and to reach vulnerable or disadvantaged communities (5). These are key factors which must be addressed if the PWID population are to be effectively engaged in HCV services and successfully treated. Bajis *et al*, as part of a systematic review completed in 2017 looking at interventions to improve engagement in the HCV care cascade among PWIDs, found no studies completed in the DAA era (117). Now that IFN and RBV free regimens offer all patients treatment options, it is key that research is undertaken to identify policies and practices that promote and improve engagement in HCV testing and treatment among this key population group.

Since the review by Bajis *et al*, positive study results have identified that equitable treatment outcomes in PWIDs, as compared with standard tertiary care clinics, can be obtained by harnessing the existing structures of the addiction services setting (121, 122). Research suggests approximately 40% of people receiving OST have HCV infection (104, 123, 124). Data from the Health Protection Surveillance Centre in Ireland reports that 80% of diagnosed cases of HCV infection report IDU as

the risk factor for infection (125). A study by Schutz *et al* assessed adherence and outcomes by utilising direct observation of DAA treatment in PWIDs receiving OST under direct observation by a nurse or physician (126). This model resulted in high adherence, with 99.8% of prescribed DAA doses received by patients, as well as high SVR rates (n=40; 100%), demonstrating that previously difficult-to-treat patients can have successful outcomes (95, 126).

A recently published systematic review and meta-analysis by Hajaiarizadeh *et al* identified that the response to DAA therapy was favourable among people with recent drug use, including those with ongoing IDU and those receiving OST, supporting broadening access in these populations (127). A Scottish study which examined the uptake of DBST and HCV treatment of patients with genotype 1 infection, in community pharmacies equipped with OST services, found this to be a feasible pathway to treatment in a population receiving OST as compared with treatment via a conventional service pathway (104). This project has now proceeded to full trial evaluation.

The removal of blanket treatment restrictions based on recent drug and/or alcohol use is also an important factor as part of the HCV treatment assessment pathway for this patient group. Previously HCV treatment was often deferred or not recommended for active PWIDs (109, 128). Providers often unjustifiably deferred HCV treatment for PWIDs because of concerns about treatment adherence, tolerability and risk of re-infection, especially in the setting of on-going drug injection (2)(128, 129). In reality, PWIDs are those who might benefit most from HCV treatment, especially since they have the highest risk of transmission to others, and can achieve SVR if adequately supported through the treatment initiation process.

Further research is required to identify points of healthcare access for PWIDs who are not engaged with addiction services and how to provide them with targeted HCV treatment services. Needle exchange programmes and community pharmacy services could help to provide access to HCV

testing and treatment in this patient group (130, 131). A feasibility study in the Scottish setting has already found community pharmacies to be a suitable setting to test and treat those on OST (104). Community pharmacies are a free advice service, with multiple pharmacies located in cities, towns and villages providing large potential population reach. They also do not require patients to make appointments and have regular daily opening hours. All of these factors make them a viable option for further research as a treatment location for hard-to-reach patients.

1.7. Resources required to achieve devolvement of Hepatitis C care strategies

Based on review of the existing research, the expansion of the HCV model of care beyond the specialist hospital setting requires education and training of HCPs working in these settings. Capacity building among HCPs is also required to ensure that available resources are best utilised to maximise positive patient outcomes in the HCV care cascade.

Healthcare resources and task shifting required for community-based HCV treatment

Workforce capacity is a key factor in expanding HCV treatment access at all levels of care. Capacity building along each step of the cascade of care, now serves as one of the biggest challenges to achieving the goal of HCV elimination (132). Examples of capacity building or task-shifting include nurse- and pharmacist-led prescribing, community pharmacist-led HCV screening, GP-led treatment management and peer-level counselling. The WHO's task-shifting guidelines for HIV care allow for non-physician clinicians, nurses, and other healthcare workers to complete tasks including managing and recognising HIV-related illnesses and opportunistic infection, initiating anti-retrovirals, managing medication complications, reviewing laboratory results, and providing patient education and counselling (133). Similar task-shifted workforce expansion is a potential pathway to expand the HCV care model in order to scale up the HCV elimination effort (134).

Task-shifting of HCV diagnosis, patient assessment and treatment to community-based GPs could expand the prescriber workforce exponentially. Multiple studies have now documented equivalent outcomes among hospital specialists and GPs.(23, 97, 135, 136) In addition, several studies of shared care between specialists and GPs, have also demonstrated success in improving access to HCV care (6–11) (137-141).

An extensive evidence base for the positive effects of moving HCV treatment beyond the remit of just hospital-based specialist clinicians, to increase treatment capacity within the healthcare setting has been seen in the management of HIV infection. Transitioning health care tasks from a limited number of highly specialised HCPs (e.g. hepatologists or infectious disease specialists) to more abundant but less specialised HCPs (e.g. GPs, nurses and pharmacists) with collaborative practice agreements, is widely adopted to manage HIV (142). Research has shown that the quality of HIV treatment by non-physicians as compared with their physician counterparts is comparable (134) (143).

However, strict protocols and guidelines are required in all healthcare environments where task-shifting practices or devolved care are implemented, based on best international and national recommendations and guidelines. A key part of this process is the provision of HCP education and support on an on-going basis. A study by Olea *et al* reported that workforce growth by 2019 will not accommodate the projected increases in the number of people living with HIV and HIV/HCV co-infection (144). Health services caring for patients with chronic HCV infection need to consider capacity building as a key step in the pathway to HCV elimination.

GP and specialist shared care model Is this section part of community-based treatment

A study completed in Australia aimed to assess the impact of a remote access specialist consultation pathway to support community GPs in treating HCV with DAA therapies (136). In the 12-month

study period, 74 participating GPs treated 114 patients for HCV infection and referred 48 patients for specialist assessment (136). No treatment failures were detected (136). The San Francisco Health Network created a secure electronic referral system to support GPs to provide community-based HCV assessment and treatment (eReferral) (97). The eReferral system provided GPs with individualised treatment consultations for each patient. This initiative resulted in a 3-fold increase in the number of patients treated for HCV in primary care (97). The service also utilised a team of HCV champions who provided on the ground advice and support to community prescribers (97).

GP-prescribing

Decentralised HCV care in Australia is an example of the model of GP-prescribing of HCV DAAs in action. Strategies undertaken in an Australian study to facilitate this model included education of primary health care providers, specialist outreach clinics to regional communities and shared care with GPs (135). SVR12 rates were similar amongst gastroenterologists (283/306, 92.5%), GPs (152/161, 94.4%), sexual health physicians (104/106, 98.1%) and other prescribers (37/39, 94.9%) (135). The provision of treatment in regional settings was facilitated through specialist visits to remote communities and the delivery of DAAs to these areas by outreach pharmacy services (135). The MDT decentralised approach used in this cohort was able to reach vulnerable populations in one of the most remote regions of Australia (135).

The fact that the patients' existing GP-based health care team were able to prescribe the DAA therapy allowed for HCV treatment within an existing therapeutic relationship, which led to improved patient engagement and DAA adherence (135). This study also demonstrated that with appropriate education and support, primary care teams can treat patients with DAA therapy for chronic HCV infection (135). An additional benefit is that these providers, through their long-term involvement with the patients, are better able to manage other major comorbidities, including

excessive alcohol consumption, smoking, illicit drug use and poor nutrition, which can have significant long term negative effects on liver and general health (135).

A prospective, observational study by Kattakuzhy *et al* in 2017, concluded that task shifting of DAA-based HCV therapy to non-specialist providers was safe and effective (145). This study is of significance as it was the first clinical trial to demonstrate high, non-inferior SVR rates among patients treated for HCV by non-specialist providers (including GPs and nurse specialists) as compared with standard of care specialist services (145). The results of this clinical trial add weight to the potential for devolvement of HCV treatment to the community setting to expand the reach of treatment programmes. Potential stumbling blocks to GP management of HCV patients which must be considered include heavy GP workloads, GP shortages in certain areas and time requirements. The importance of support resources and national guidelines around testing and treating cannot be understated. In the case of HCV studies undertaken with the GP services in Australia, these practices often have pre-existing similar frameworks for management of HIV patients, meaning they have a pre-existing skill base around caring for patients with a complex condition, something which GPs in many other regions of the world do not (146).

Another pathway of devolved treatment access or shared care treatment, is the role of non-physician healthcare professionals in delivering HCV care. In some settings, there is a shortage of clinicians to manage and treat HCV infection and this gap in the health care system is an opportunity for increased involvement by clinical pharmacists and nurses. This represents a more cost-effective model and could widen the pool of potential practitioners which would provide greater reach for HCV treatment programmes towards hard-to-reach and marginalised patient groups (134).

Nurse-led HCV treatment in primary care

Nurses have been a prominent member of the HCV MDT since initial therapy with IFN in the 1990s (147). Their roles within the specialist treatment team have been well described (148, 149).

In the DAA era, examples of nurse-led community-based HCV care have been described (150-152). For example, a 2018 study by Wade *et al*, conducted in Australia and New Zealand, compared standard tertiary centre HCV care with community-based, nurse-led care (153). Preliminary findings from the on-going study reported 67% treatment uptake in the primary care setting versus 44% treatment initiation in the equivalent tertiary care site with similar treatment outcomes in both patient groups (154). However, this study did not provide detail on the level of training received by community-based nurses prior to participation in the study.

In the US, a 2015 study by Kattakuzhy *et al* completed a similar assessment as a non-randomised open-label clinical trial. All providers underwent three hours of training based on best practice international HCV guidelines. Patients included in the study received treatment with SOF/LDV. Patients achieved an overall SVR rate of 86% (N= 600) (145). SVR rates were comparable across the three provider arms, nurse prescribers (89.3%), GPs (86.9%) and HCV specialists (83.8%) (145). A limitation with this study was the non-randomisation of patients into the respective study arms which may have introduced bias. In addition, all patients recruited into the study were treated with the same DAA regimen, SOF/LDV, thus removing the vital step of optimum DAA regimen selection from this assessment of comparable outcomes among differing prescriber types. Management of patients who failed treatment and those lost to follow up was also not presented. However, the study does highlight that HCV treatment administered by non-specialist providers is safe and effective and should form part of the solution to bridge existing gaps in the continuum of care for patients with HCV infection (145).

Pharmacist-led HCV treatment in primary care

HCV programmes need team members who are knowledgeable in medication selection, procurement, medication adherence, medication reconciliation, drug-drug interactions (DDIs), laboratory monitoring, and patient follow-up. In the HCV outpatient care setting, a clinical pharmacist can implement all of these interventions (22). As medication experts with training in HCV management, clinical pharmacists are in a unique position to increase access to care and improve health outcomes for patients with a HCV diagnosis (155).

To adapt to staff shortages at a clinician level, many treatment settings in the US have developed practice collaborative agreements with pharmacists (155). Practice collaborative agreements allow pharmacists to provide HCV care to patients under the supervision of a specialist physician. The additional responsibilities of the pharmacist, beyond their existing roles in HCV care, include ordering and interpreting laboratory tests, selecting the optimum DAA regimens and duration of therapy and management of treatment related side effects (155).

This type of capacity building through shared care between GPs and pharmacists is described in a study by Mikolas *et al* which examined the potential role of a pharmacist-clinician collaborative practice model in a cohort of US Veterans (156). This care model permitted specialist pharmacists to initiate and manage all aspects of HCV treatment in a designated patient population. Pharmacist interventions included pre-treatment assessment, DAA regimen selection, patient education, drug therapy monitoring during treatment, including addressing any issues relating to adherence and post-treatment follow-up, to check SVR results (156). The overall SVR rate was 94% across all DAA regimens utilised and levels of cirrhosis present (156). The results were comparable to SVR data from DAA clinical trials and thus suggest that this collaborative care model could be effectively utilised to expand the HCV model of care (156).

Another benefit displayed by this study was a reduction in the length of physician consult times from 40 to 15 -20 minutes as HCV treatment patients were reviewed by the specialist pharmacist, thus freeing up the limited time resource of the doctor to see other patient groups (156). A strength of this study is that it included difficult to treat patient groups including cirrhotic patients and treatment experienced patients whom to date have often been excluded from expanded model of care studies. This collaborative care model achieved comparable SVR rates in these patient groups to DAA trial outcome data (156). However, it should be noted that these specialist pharmacists are experts in the area of HCV patient care and if treatment is to be devolved to community based care, pharmacists with such specialist knowledge would not be readily available (156). This limits the applicability of this study findings to HCV treatment by pharmacists in a devolved care setting.

Other studies have examined the level of pharmacist involvement in HCV patient care and the follow-on impact of SVR rates. A study by Love *et al* evaluated the practice of alternating clinic reviews by physicians and pharmacists (157). A study by Naidjate *et al* found that there were no significant differences in outcomes between patients receiving care at the pharmacist-run HCV clinic and the physician-led, pharmacist-assisted clinic (158). A pharmacist – led clinic means that the pharmacist completed all parts of the patient’s clinic visit. A pharmacist-assisted clinic means that the pharmacist completed some parts of a patient’s clinic visit in conjunction with a physician. These study findings add weight to the idea that both pharmacist-managed and pharmacist-assisted clinic models may be reasonable alternatives for providing outpatient HCV care as part of a task shifting model of care or in areas with limited clinician resources (158). However, again these studies did not provide details on management of patients who failed treatment or were lost to follow up. Were there any differences in the patients who failed or discontinued treatment between the pharmacist managed or physician managed patients?

Pharmacists have also been involved in providing education and training as part of multiple education models previously described (96, 159). One US study which examined education of staff working in a large safety net health system described the role of a lead pharmacist in infectious diseases who trained all pharmacists within the institution in the area of HCV.(107) A MDT collaborative was then created at each HCV clinic with the primary care HCV specialist and an on-site pharmacist (107). This pharmacist training then facilitated completion of on-treatment reviews by members of the pharmacist team with patients taking DAAs (107).

The Pharmacy Guild of Australia developed a free online course, “Management of Hepatitis C and the role of pharmacy” (160). The course provides education relating to the pathophysiology of HCV, the availability of DAAs as treatment and the role of pharmacists in optimising patient screening, treatment access, DAA adherence and risk reduction strategies (160). This education module was funded by Gilead. In the UK and Ireland, a free online learning resource, My HepEd®, was developed consisting of training modules relating to HCV virology, anatomy and DDIs (161). This learning resource is funded and maintained by AbbVie®.

Pharma-funded educational materials or meetings can occur in the healthcare setting. With very limited funding available from national healthcare services for continual professional development and training, many healthcare professionals’ avail of these pharma-resources. However, regulations and good practice require the detachment of commercial activities from medical activities within pharmaceutical organizations. The Irish Pharmaceutical Healthcare Association (IPHA) transfer of values register, launched in 2016, is part of an initiative of the European Federation of Pharmaceutical Industries and Associations (EFPIA). Ideally, given that eradication of HCV infection is a WHO target, healthcare systems should be requested and encouraged to fund and develop national HCV learning resources within the existing healthcare services.

1.7.1. Education and training in an expanded model of HCV patient care

The workforce development activities that accompany any changes to, or implementation of, new models of HCV patient care, must be re-enforced by protocols and healthcare practitioner education and training. A survey of primary care physicians completed in 2016 found that the majority (70%) did not feel up to date on current HCV treatment options and most were unaware of the potential for SVR rates >90% with new DAA regimens (95, 162). As HCV patient care may be a completely new role for some HCPs it is key that education resources are available for, and tailored to, specific HCP roles and based on the context of the service provision within which they will practice.

Previous research in the area of healthcare professional education around HCV patient care has shown that primary care providers were empowered through education programmes, upskilling and shared-care models to prescribe community-based treatment, enhancing their skill mix and job satisfaction (135). Examples of educational resources developed and utilised in the HCV care setting include e-learning modules, face-to-face lectures, one-on-one teaching sessions, virtual clinic case discussion and peer-to-peer learning schemes.

The content of staff education materials must be flexible to cater for a wide range of pre-existing experience and learning needs. Another valuable tool in the area of staff education is the identification of local champions within specific healthcare professions or practice settings (82). A US study by Facente *et al* described the benefits of local HCV champions in terms of providing on-going support and training to community HCPs in the context of their area and level of practice (97). Use of HCV champions is an intervention which has the potential to be sustainable and scalable which is key in the expansion of devolved HCV treatment services.

One example of an education initiative is HepCare[®], funded by the EU, which provides education and support to physicians and patients within a treatment centre network across a number of sites in the EU, including Ireland (163). Research of multi-layered models of care for HCV management in other countries with a similar incidence and prevalence of the virus, including Australia, have also shown the benefits and possibilities for increased screening, linkage to care and treatment initiation when HCP education programmes are implemented (114, 164).

Ochalek *et al* utilised an e-learning module to provide education and training to a HCV healthcare team. The educational intervention was associated with significant increases in knowledge ($p < .001$). These improvements persisted and increased throughout the study ($p < .001$) (165). As part of initiation of GP prescribing of DAAs in Australia in 2016, a study by Wade *et al* described the education resources provided to the community healthcare teams (136). Education and training provided included peer-based teaching, case presentations, group work, demonstration of available online resources and on-going specialist support (136).

A MDT learning model has also been described in several studies (97, 107). A MDT structure allows for the development of an interdependent learning environment engendering on-going training and support of MDT members. A case report by Sokol *et al* described implementation of a MDT team-based approach for treating chronic HCV infection at multiple primary care sites across a large safety net health system (107). An infectious disease specialist visited primary care sites, training two HCPs at each centre to become primary care HCV specialists who then provided teaching and support to the wider primary care team (107).

An example of an innovative education intervention in HCV care which was initiated in the United States, is Project ECHO. The Project ECHO (The Extension for Community Healthcare Outcomes) model is an example of a successful education intervention developed to deliver complex speciality

medical care to patients with chronic HCV infection undergoing treatment in resource poor settings (159). The project, was designed to educate, train and support primary care practitioners in developing knowledge and competency to treat HCV infection (159). However, few of these studies were prospective or comparative, and all used IFN-based regimens, limiting their applicability to current practice.

The VA medical service in the US implemented an amended format of the ECHO programme named VA-ECHO (96). This consisted of the provision of video-conferencing with HCV specialists when required. A study by Beste *et al* found that the rate of primary care provider initiated antiviral medication was 21.4% among treated patients reviewed on VA-ECHO teleconferences compared with 2.5% among unexposed patients ($P < .01$) (96). National implementation of VA-ECHO was positively associated with HCV treatment initiation by primary care providers, without differences in sustained virologic response (96).

An early systematic review published by Brew *et al* in 2013, found that there was emerging evidence supporting the effectiveness of anti-viral treatment provision for patients with chronic HCV in a wide variety of primary care and wider community settings. Both clinical trial and real-world data have demonstrated the remarkable progress in efficacy, safety, tolerability, shortened treatment durations, and pan-genotypic efficacy of currently available DAAs (54, 57, 64, 69, 166). However, there are still a need for further randomised clinical trials in the area of DAA therapy in the community setting.

Model of care research and development

A research focus on new methods of care delivery to improve outcomes for patients with HCV infection, is needed, to ensure that ongoing improvements to the HCV care cascade occur, to drive HCV testing, diagnosis, linkage to care and treatment uptake. This point links back to one of the

core WHO recommendations, of integration of hepatitis testing, care and treatment with other services (5). Research is required to identify evidence-based interventions which can be incorporated into an expanded and integrated model of care for HCV to more effectively deliver treatment and maximise treatment outcomes (167).

While the studies discussed here report the outcomes of HCV patient care by multiple HCPs, including doctors, nurses and pharmacists, this research project will focus on the potential for pharmacists to further contribute to the evolving model of HCV patient care. Considering specifically the studies discussed here in relation to pharmacist interventions they do not give detail on the specific key pharmacist roles within the HCV cascade of care, their impact on DAA treatment outcome and the education and training required to perform pharmacist tasks.

This research project will aim to add more detail on specific pharmacist-led interventions to the evidence base including findings relating to the role and importance of medication reconciliation and DDI review and how they should be incorporated into devolved HCV care models. Given the breadth of clinical roles that pharmacists fulfil as part of the HCV care cascade, their potential roles in the expanded care model warrant further investigation and development. Further research into the role that pharmacists can play in providing education and training among HCPs involved in HCV patient care, including doctors and nurses is warranted.

1.8. Development of speciality pharmacy services and practices in all areas of healthcare in Ireland and internationally

Specialty pharmacy services are increasingly used across a variety of healthcare settings to enhance patient outcomes and improve the quality of care provided (168). Examples of pharmacist activities include medication counselling, medication reconciliation, drug regimen selection and dosing

advice, DDI review, renal and hepatic medication dose adjustment assessments, medication adverse effect management, and medication adherence counselling and monitoring.

1.8.1. Speciality pharmacy services in other healthcare specialities

There is significant literature available detailing the clinical and cost benefits of pharmacist-led activities in multiple clinical specialities including HIV, epilepsy, kidney disease and oncology (169-171). Numerous studies have also repeatedly demonstrated positive outcomes from pharmacist management of many chronic disease states, such as diabetes, hypertension, lipids, asthma, and congestive heart failure (156). Integration of the pharmacist into the MDT structure supports expansion of the role of the pharmacist in these settings by creating the opportunity for pharmacist-driven initiatives, such as drug protocol development and implementation, and laboratory ordering and monitoring (168).

HIV patient care

In an 18-month prospective cohort study of 90 HIV-infected patients, Molino *et al* identified that the number of drug-related problems per patient decreased significantly from 5.2 to 4.2 (19.2% reduction) after the intervention of a clinical pharmacist (172). In Spain, research conducted by Diaz *et al* found that outpatient pharmaceutical care prevented 231 drug-related problems in 184 patients over a 15-month period. This study was mainly performed in HIV-infected patients (49.8%) and patients with kidney disease (22.1%). The most frequent drug-related problems identified were DDIs (26.0%), followed by prescription errors (15.6%) and medication non-adherence issues (15.6%)(173).

Haematology/Oncology

One study including 249 oncology patients who were assisted through a pharmaceutical care programme with three clinical interviews over a 6-month period demonstrated an increase in the

percentage of patients with a medication adherence rate of greater than 90% in the intervention group compared with the control group (from 60.5% to 80.8%) ($P < .001$). This programme identified 275 medication errors and 362 pharmacist interventions, mainly to reinforce patient education (174).

General Outpatient Department setting

Viktil *et al* completed an assessment of pharmacist activity in general medicine and rheumatology outpatients (N = 727) and demonstrated that interventions by the clinical pharmacist led to significantly more medication-related problems being identified than with usual care (from 4.4 to 2.4 problems identified per patient in the intervention and non-intervention groups, respectively; $P < .01$) (175).

A systemic review of pharmacist-led medication therapy management (MTM) interventions in the outpatient setting was undertaken by Viswanathan *et al* in 2015 (176). MTM was defined as a strategy for delivering a variety of non-dispensing clinical pharmacy services to patients and their clinicians (176). The review concluded that there was insufficient evidence to determine the effect of MTM interventions by pharmacists on most evaluated outcomes (e.g., drug therapy problems, adverse drug events, disease-specific morbidity, disease-specific or all-cause mortality, and harms) (176).

Specifically, MTM interventions improved medication appropriateness (as per the medication appropriateness index; $p < .001$), adherence (approximately 4.6%), and the percentage of patients achieving a threshold adherence level and reduced medication dosing (176). Pharmacist-led interventions led to reductions in health expenditure on medications, although it should be noted that the studies included reported wide confidence intervals (176). Pharmacist-led interventions were found to lower the odds of hospital admission and the costs associated with hospital inpatient

stays in patients with diabetes and heart failure (176). The degree to which pharmacist-led interventions identified and resolved medication-related problems which translated into consistent, detectable improvements in biomarkers of morbidity, health, patient experience, use, and costs could not be determined from by this systematic review (176). Given the heterogeneity of study designs a lack of robust evidence for pharmacist interventions was identified.

1.8.2. Hepatitis C: Treatment and the role of the specialist pharmacist

The management of HCV infection is centred on pharmacotherapy, making the clinical pharmacist a key part of the patient's MDT (22). The pharmaceutical care processes involved in the care of patients with chronic HCV infection treated with DAA regimens are complex and multi-layered. Pharmacist-led interventions encompass initial completion of medication reconciliation and DDI review at pre-treatment assessment right through to the end of treatment and post treatment follow-up visits. During this time, several important pharmacotherapeutic interventions occur which aim to optimise the safety, efficacy and cost effectiveness of HCV treatment received by each patient.

Current HCV guidelines provide recommendations on its diagnosis, treatment, and management (60, 61). Specific recommendations involving clinical pharmacists in HCV care do not exist (22). Practice guidance on the potential roles of the pharmacist in HCV care have been published in the US (22). The US Department of Health and Human Services, identified pharmacists as key stakeholders in the continuum of care of those living with viral hepatitis in their Action Plan for Viral Hepatitis in 2014 (177). The plan identified the need to provide on-going training to clinical pharmacists to monitor the management of patients receiving hepatitis treatment (177). The action plan also discussed the importance of research work around extended community models of care for hepatitis treatment and the need for further research to describe effective care models (177). However, in the most recent version of the US National Hepatitis Action Plan (2017-2020), there

are no references to pharmacy services within the text of the document (178). The European Association for the Study of Liver Disease (EASL) and the Australian Clinical Practice Guidelines for Hepatitis C make one reference to the role of pharmacists in relation to the identification of potential DDIs (60, 179). No published guidance on the pharmacist role has been defined in any other international setting.

However, there have been multiple individual studies describing the varied pharmacist-led roles and responsibilities in HCV patient care. Publications identified relating to pharmacist interventions in HCV care can be divided into two categories, interventions relating to pre-DAA treatments based on IFN-containing regimens, and interventions relating to DAA treatment regimens.

The role of the pharmacist in the IFN/RBV era

While no longer used in HCV therapy, the evidence generated in this era began to describe the pharmacist activities in HCV patient care and the value these interventions added (Table 1.2). Effective medication counselling by pharmacists has been shown to positively impact patient adherence to HCV therapy in previous studies involving the use of IFN and RBV (22). In 2005, Kolor *et al* described a pharmacist-managed HCV clinic at a VA Hospital in the US where specially trained pharmacists provided extensive medication counselling and patient education at initiation of treatment and at follow-up visits (180).

In 2007, Smith *et al* published a pilot study that retrospectively evaluated outcomes in a pharmacist-managed HCV clinic at the Los Angeles Department of VA Healthcare System (181). Patients were referred to the pharmacists by the evaluating physician. Pharmacists completed an initial appointment with each patient to discuss the proposed treatment plan, explain medication administration and to provide education and support regarding chronic HCV infection. The clinical pharmacist followed patients with monthly visits and laboratory tests to monitor for HCV treatment

response and adverse reactions. The pharmacist worked under the supervision of a gastroenterologist (181). Overall, 17 of the 27 enrolled patients (63%) achieved a SVR. The authors concluded that their clinic was able to achieve a SVR rate comparable to that of physician-run clinics, while also efficiently providing patient support and education (181). A major limitation of this study was its lack of a comparison group without pharmacist involvement. Additionally, there may have been bias in the selection of motivated patients for this pilot study, resulting in a higher SVR rate and no patients lost to follow-up. Adherence assessment was not performed. Nevertheless, the study provided, for this first time, information about detailed and potential broad-ranging responsibilities for the pharmacist working in the HCV clinic setting (181).

In 2009, Mariño *et al* presented the results of their study assessing the impact of pharmacists on the management of patients with chronic HCV genotype 1 infection, in a hospital in Spain (182). A convenience sample of 50 treatment-naïve patients initiating therapy with IFN and RBV received consultations from pharmacists throughout the entire course of therapy. Pharmacists provided medicines information, education about potential adverse drug reactions, advice on medication storage, drug administration, and management of missed doses. These visits were provided in tandem with attending the hepatologists at the study site (183).

In 2012, a US study from the VA healthcare system provided the first description of the integration of a clinical pharmacist specialist into an existing HCV clinic and described an extended list of pharmacist-led activities beyond just patient education and medication counselling (157). This study described pharmacists' activities involving patient education, DDI management, adherence assessment, side-effect management, and medication dosage adjustment. However, these pharmacist-led interventions were not discussed in terms of impact on treatment outcome for patients in the findings of this study.

A role in which pharmacists had key input into in the era of IFN/RBV with telaprevir, boceprevir and simeprevir use, was the implementation of response guided therapy and DAA stopping rules. During use of first- and second -generation protease inhibitors, telaprevir, boceprevir and simeprevir, clinical pharmacists ensured that patients who met the stopping rules (e.g. HCV viral load > 1000 IU/ml at week 4 of treatment with IFN/RBV/telaprevir) discontinued treatment to prevent needless drug exposure, minimise development of DAA resistance, avoid treatment related side effects and to ensure cost efficiencies (22).

Table 1.2 The roles of the pharmacist in the care of patients with HCV infection

Pharmacist roles	
Patient education	Drug-drug interaction assessment and management
Medication counselling	HCV medication dosage adjustment
Assessment of HCV treatment response	Implementation of HCV treatment stopping rules (telaprevir, boceprevir, simeprevir and IFN/RBV)
Adverse effects management	Managed of re-retreatment post DAA relapse or re-infection
Medication adherence assessment	Medication procurement
Management plan for missed or late medication dosages	Screening and validation of HCV DAA prescriptions
Participation of HCV MDT	Ordering and interpreting laboratory results

HCV: Hepatitis C; IFN: interferon; RBV: ribavirin; DAA: direct acting antiviral; MDT: multidisciplinary meeting

The role of the pharmacist in the DAA era

Descriptions of the multiple potential roles of pharmacists in the treatment of patients with chronic HCV infection have been published in scientific publications in the era of DAA therapy (Table 1.2).

The GRUViC project by Chamorro-de-Vega *et al*, completed at a tertiary care hospital site in Spain examined the impact of implementation of a comprehensive pharmaceutical care programme (CPCP) on outcomes for patients treated for chronic HCV with DAA based therapy (N =1070) (184). DAAs in use during the study period were P/rOD, SOF/LDV, SOF, simeprevir and DCV, with or

without RBV. The CPCP listed a set of specific interventions including validation of HCV DAA prescriptions, detection of DDIs and adverse effects of treatment and patient education (184). The study employed an MDT system including weekly meetings between hospital pharmacists and physicians and a consultation circuit with other hospital clinical services and primary care (184). This study identified that the implementation of a CPCP developed by hospital pharmacists in patients treated with DAAs for HCV infection is an effective approach that improves patient safety (184).

A study by Olea *et al* (N = 135) in 2018, described the role of the pharmacist in the care of patients with HIV/HCV co-infection (144). The clinical pharmacist's role included medication adherence counselling, DDI screening, counselling regarding common treatment side effects , counselling regarding HCV treatment outcomes and risks of reinfection, ordering of laboratory tests and interpretation of HCV laboratory values (144). A MDT met weekly to discuss patient updates and recommendations. A collaborative drug therapy agreement allowed the clinical pharmacist to prescribe medications to counteract adverse effects, prescribe and dispense antiretrovirals and other chronic medications, and to order laboratory tests. The study authors concluded that a clinical pharmacist's expertise as part of a MDT care team facilitated optimal treatment outcomes and provided critical support in the management of DAA therapy in individuals living with HIV/HCV coinfection (144). There are many considerations when treating patients living with HIV/HCV coinfection and results from this study suggest that clinical pharmacists' expertise plays a defined and critical role (144).

Patients have supported the inclusion of a clinical pharmacist in healthcare teams and have reported high levels of satisfaction with clinical pharmacists when they were involved with HCV treatment. In a satisfaction survey, patients reported 100% satisfaction with the clinical services provided by the pharmacist, including time spent during visits, medication adherence counselling, and education on HCV disease state, medication storage, and administration (185).

Pharmacist-led interventions have developed from patient education, adherence monitoring and side-effect management, primarily in the era of IFN-based regimens to DDI review, tele-medicine clinics, optimisation of workflow and education of HCPs in the DAA era (182, 186). Key interventions including medication reconciliation, HCV treatment regimen selection and optimisation and DDI identification and management and, on treatment monitoring are now vital tasks which promote optimum treatment outcome.

1.9. Expansion and development of the role of the pharmacist as part of an expanded model of HCV patient care

All HCPs involved in the care of HCV patients have the potential to contribute to evidence-based interventions which can improve patient care and treatment outcomes. Current HCV guidelines provide recommendations on its diagnosis, treatment, and management. However, specific recommendations involving the role of clinical pharmacists in HCV care are not available to date (22).

When a patient is being assessed for HCV treatment there are multiple patient factors that must be considered including the level of liver fibrosis present, HCV genotype and viral load, previous HCV therapies received, co-morbidities such as presence of any renal impairment, co-medications and patient medication compliance. All of these factors influence the choice of DAA therapy for an individual patient. DAA factors which must be considered include the potential for drug-drug interaction (DDI), suitability of the DAA regimen for use in decompensated cirrhosis or renal impairment in addition to pill burden, potential for side effects and the impact of HCV resistance on treatment efficacy. All of these factors come together to impact the chance of achieving SVR. Within individual healthcare systems, preferred or first line DAA regimen use must be adhered to, along with ensuring patient eligibility for treatment access should any restrictions be in place in practice.

We know, as previously described, that pharmacists perform many of these processes and interventions along the complex and often disjointed care pathway for HCV patients as they are assessed for, and proceed through, HCV DAA therapy. Pharmacist-led activities, both as part of pre-HCV treatment assessment and during HCV DAA therapy play a role in the successful treatment of patients with HCV infection. As the model of care for HCV in Ireland and internationally continues to evolve and develop it is timely to better describe and define the pharmaceutical care roles within the MDT process and their clinical impact.

Since 2014, the knowledge and skill base among hospital-based pharmacists in Ireland, involved in the care of patients with HCV, has grown and developed. In Ireland, we now possess a team of specialist HCV pharmacists within our tertiary care system. A necessary step in achieving a devolved model of HCV care requires the development of pathways to disseminate this knowledge among our community-based healthcare partners, to ensure HCV treatment is expanded to all patient groups in need. As part of a national plan, funding was provided to roll out DAAs in the hospital outpatient setting.

Evaluation of novel interventions aiming to facilitate scale-up of DAA interventions is needed. Such research will allow for evaluation of different treatment models with the aim of optimising HCV treatment and outcomes among all patient groups. Different intervention types are needed given the highly diverse mix of patients requiring HCV therapy across healthcare settings (112).

The pharmaceutical care process for HCV patients follows a logical sequence from initial completion of medication reconciliation at the pre-treatment assessment clinic visit to end of treatment. During this time several important pharmaceutical care interventions occur which aim to optimise the safety, efficacy and cost effectiveness of HCV treatment received by the patient. Could these pharmacist-led interventions be combined into a complex intervention toolkit? Would this help

with devolvement of pharmacist roles to those practising in community settings? Healthcare interventions which aim to facilitate this process and form part of the HCV model of care must demonstrate an impact on clinical outcomes. In addition, any interventions introduced must be sustainable and adaptable to all HCV care settings.

Complex intervention tools have been utilised in multiple healthcare specialities including oncology, emergency medicine, medication safety, surgery and venous thromboembolism (VTE) risk assessment. Development and implementation of intervention tools has been described in many healthcare states. Indeed, there has been much research in justifying the implementation of treatment pathways as they lead to consistent care standards, lower healthcare costs, and positively influence outcomes of care (187). A study by Vandael *et al* reports the development and validation of an algorithm which adopted a weighted points-based system to manage the risk of QTc-prolongation in the community pharmacy setting (188). In another example, Na *et al* reported the development of an integrated and evidence-based treatment algorithm to standardise drug therapy management for chronic kidney disease patients (189). The final algorithm incorporated information from Kidney Disease Improving Outcomes guidelines and spanned all aspects of the patient's pharmaceutical care, whether inpatient from admission to discharge or outpatient, including medication reconciliation, medication evaluation and management, discharge pharmaceutical transition and ambulatory pharmaceutical transition services (189).

A study by Jaehde *et al* applied a specific multi-step intervention tool as a medication safety system in the oncology setting (190). By implementing specific interventions, the aim of this research was to reduce the incidence of adverse effects and enhance medication adherence.(190). The widely cited Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) tools, which completes a medication review for elderly care patients, have measured the impact of the tools on downstream healthcare outcomes, in this case, the time to re-

admission of elderly patients (191, 192). Significant and sustained improvements in prescribing appropriateness in terms of reducing the rates of overuse, misuse and underuse of medications were identified(192).

Given the multiple steps involved in the HCV patient care pathway from patient identification, diagnosis, assessment, to treatment initiation and completion, the process fits the definition of a complex healthcare system or process. A literature search for use of complex interventions in HCV patient care identified a single study which considered the development of a novel complex intervention to aid optimum treatment uptake and outcomes in an expanded HCV model of care, undertaken by healthcare researchers in the Tayside region of Scotland (104, 193, 194). This research group has sequentially developed integrated HCV treatment services over the last two decades, moving from standard secondary care-based hospital outpatient services, to nurse-supported treatment services, then to a HCV managed care network including a DBST programme in drug treatment services and development of community based treatment services (83, 194-197).

The SuperDOT-C study by this research group is assessing the impact of utilising the existing community pharmacy environment and associated therapeutic relationships to smooth the pathway into HCV treatment and to facilitate co-administration of OST (methadone and buprenorphine/naloxone) and HCV DAA therapy, under the supervision of the community-based pharmacist (197). The conventional model of care in Scotland would require referral and attendance of patients at a specialist treatment site where they could be assessed and treated.

This SuperDOT-C study aimed to see if a community pharmacist-led treatment programme would impact testing and HCV treatment uptake rates, through a simplified care pathway for patients with genotype 1 infection (104). All pharmacy staff involved with the study received training on good clinical practice, study procedures and documentation and were integrated into the pre-existing managed care network (197). The pharmacist completed a pre-treatment checklist of co-

morbidities, medical history and concomitant medication. The fibrosis-4 index for liver fibrosis (FIB-4) scores were calculated based on blood tests completed by a local phlebotomy service for these patients. Prescriptions for HCV treatment were written by an independent pharmacist prescriber. In patients with potential contraindications including the presence of cirrhosis or pharmacist concerns about patient suitability, the pharmacist could refer to a central clinical for medical review. Patients received HCV treatment based on the pattern of their OST collection (for example, twice weekly attendance or daily attendance) (104).

The study followed the key UK Medical Research Council (MRC) framework development steps along the pathway to designing the complex intervention. This included the construction of a logic model to explicitly identify targets for evaluation and data collection (194). Service user and staff feedback was sought during the study period. Staff considered that strong leadership and involving all the pharmacy team were necessary prerequisites for success (104). The intervention was less successful in areas where this was lacking (104). Staff enthusiasm for these new roles and positive relationships with patients were also important factors in uptake of HCV treatment via this pathway (104). Sufficient staff was seen as essential, with less tests completed in pharmacies where the staff felt under pressure because of existing workloads (104). In pharmacies with strong patient relationships, the service was seen as part of the range of ways that the health of the patients was improved. The patient assessment was felt to be straightforward and easy to accomplish (104). Barriers identified to treatment uptake via this pathway included off-site phlebotomy and staffing limitations (104).

This study provides evidence that community pharmacies can successfully provide HCV testing and treatment to patients attending for OST and that this is a feasible treatment model (104). More participants accepted HCV testing and treatment in this novel pharmacist-led pathway than in the conventional specialist centre care pathway; the difference between the two pathways and their

HCV testing acceptance rates was found to be statistically significant (<0.01) (104). Results from an interim analysis of this research reported that 251 patients were recruited into the study with 99 attending for treatment via the conventional pathway and 152 via the community pharmacy pathway. This interim result highlights that the community pharmacy as a pathway to HCV treatment is more attractive to patients than the current pathway of GP or hospital clinic-led HCV care. The work undertaken in this study, has confirmed that the local nature of the pharmacy service and the pre-existing reasons for attendance are key mechanisms in recruitment patients for HCV testing and treatment via this pathway (104).

Limitations of this study include a lack of description of exact levels and types of staff training and resources provided in order for community pharmacists to participate in this study. In addition, the study only considered treatment of genotype 1 patients and only examined the impact of this community-based treatment model in patients engaged in an opioid substitution programme.

Can a HCV specific complex intervention toolkit which incorporates all key patient and disease factors along with international treatment guideline recommendations which is developed, validated, implemented and impact assessed has the potential to support the devolvement of DAA based therapy to secondary and primary care services? Can a novel complex intervention toolkit, incorporating pharmacist-led interventions facilitate healthcare professionals in selecting the optimum HCV treatment regimen when assessing patients for HCV treatment?

1.10. Research Aims

This research project aims to describe the role and impact of pharmacist-led activities in HCV patient care and to evaluate real-world use and outcomes when these activities are developed into a novel complex intervention toolkit. A two-phase approach was undertaken, the first of which involved literature review and assessment of the roles and impact of pharmacist-led activities in HCV infection (Figure 1.3). The findings from phase one will guide the design, development, optimisation and evaluation of a novel complex intervention toolkit based on pharmacist-led activities in HCV patient care which aims to ensure optimum HCV DAA prescribing and treatment across all models of care.

Overall research aim: To assess the impact of a novel complex intervention toolkit, designed to facilitate healthcare professionals in selecting the optimum HCV treatment regimen for each individual patient based on specific characteristics and international best treatment guidelines.

Research Outline	
<p><u>Part 1</u></p> <p>Study 1 - Medication reconciliation</p> <p>Study 1a - Clinical significance of medication reconciliation variances</p> <p>Study 2 - Complementary and alternative medicines (CAM) among HCV seropositive patients</p> <p>Study 3 - DDIs between patient co-medications and DAAs</p> <p>Study 4 - Patients with chronic HCV infection and co-morbid epilepsy treated with DAAs</p>	<p><u>Part 2</u></p> <p>Study 1 - Design, development and optimisation of the Hepatitis C pre-treatment pharmacist assessment (PTPA) toolkit</p> <p>Study 2 - Feasibility and acceptability of the PTPA complex intervention toolkit</p> <p>Study 3 - PTPA Pilot Study</p> <p>Study 4 – PTPA Evaluation Study</p>

DDIs: Drug-drug interactions; DAA: Direct acting antiviral; HCV: Hepatitis C PTPA pre-treatment pharmacist assessment

Figure 1.3 Research phases

Project Objectives

1. Literature Review:

- ✓ To identify published evidence of the role of pharmacist-led interventions in the care of patients treated for HCV and parallel pharmacist roles in other disease states.
- ✓ To identify existing literature around use of complex interventions in healthcare, and where available in HCV patient care.

2. An assessment of the pharmacist-led process of medication reconciliation and DDI identification, assessment and management in a HCV outpatient clinic service practice.

- ✓ Identify and quantify medications in use in a study population, using the process of pharmacist-led medication reconciliation.
- ✓ Compare the list of medications identified through pharmacist-led medication reconciliation with the medication list documented in the patient medical notes and categorise any variances identified.

- ✓ To obtain peer review of episodes of medication variance identified as part of the HCV medication reconciliation process with assignment of risk ratings using a validated tool for scoring the severity of medication errors, the Visual Analogue Scale.
 - ✓ Assess the prevalence, type, and severity of DDIs between DAAs and identified patient co-medications.
 - ✓ Describe pharmacist-developed DDI management strategies
 - ✓ Assess the rate of acceptance, among prescribers, of the pharmacist-developed DDI management strategies
3. An assessment of patient knowledge and attitudes towards complementary and alternative medicines among HCV seropositive populations
- ✓ To identify, quantify, describe and categorise use of complementary and alternative medicines among a HCV seropositive patient population at a hospital outpatient clinic.
 - ✓ To measure patient perception about complementary and alternative medicines use among a HCV seropositive patient population.
4. HCV DAA treatment options in patients with epilepsy, a matched-cohort study.
- ✓ To assess the prevalence, severity and management of potential DDIs identified as part of HCV pre-treatment pharmacist assessment and to measure the impact of DDIs between DAAs and epilepsy medications on the timeline to HCV treatment initiation.
5. Development and evaluation of a complex intervention toolkit based on pre-treatment pharmacist-led activities in HCV infection
- ✓ To develop a process map of pharmacist-led interventions in Hepatitis C patient care.
 - ✓ To identify key pharmacist-led interventions for inclusion in the pre-treatment patient assessment complex intervention toolkit.
 - ✓ To describe the design, development and optimisation of a novel complex intervention

toolkit.

- ✓ To refine the understanding of how the intervention works and facilitate ongoing adaptation of the intervention design in preparation for a full evaluation.

6. Evaluation of the Pre-Treatment Pharmacist Assessment (PTPA) complex intervention toolkit

- ✓ This study aimed to provide information on the validity of the pre-treatment patient assessment complex intervention toolkit in helping healthcare professionals chose the optimum HCV treatment regimen selection for specific patients.
- ✓ To determine healthcare professional perceptions and opinions on the pre-treatment patient assessment complex intervention toolkit use in healthcare and its potential for use in HCV treatment.

Chapter 2: Pharmacist-led interventions in Hepatitis C patient care:

Medication reconciliation and drug-drug interactions

2.1. Medication reconciliation and drug-drug interactions

2.1.1. Introduction

Medication reconciliation

Medication reconciliation is defined as 'the process of obtaining a complete and accurate list of a patient's current medications from all available sources at all points of contact and verifying and reconciling medications to reduce medication errors' (198). Medication reconciliation is a key strategy in reducing medication errors thus improving patient safety (199). Studies have shown that more accurate and comprehensive medication histories are obtained by pharmacy personnel as compared with other health care professionals (168).

Studies to date have advocated the beneficial effects of medication reconciliation at the point of hospital admission, for both patient safety and clinical outcomes (200-202). Little if any work has been completed to describe or measure the occurrence and outcomes of medication reconciliation processes in an outpatient setting (203-205).

In the area of HCV therapy there are now multiple treatment options for a patient population whom often have multiple co-morbidities and are prescribed significant numbers of concomitant medicines. However, to date there has only been one conference abstract published examining the rate of medication discrepancies when medication reconciliation is completed with HCV patients in the outpatient setting (206). In the case of other studies published in the area of pharmacist-led interventions in HCV patient care, the process of medication reconciliation may have been undertaken, however it has not been described or quantified in terms of impact by any other researchers in any publications or conference abstracts to date. No studies investigating the process,

significance and clinical outcomes of pharmacist medication reconciliation for patients receiving HCV therapy in an ambulatory care setting have been published to date. Given that most patients receive treatment for HCV in the outpatient setting, it is imperative for patient safety that the process of medication reconciliation is made an integral part of the patient care plan.

A key follow on benefit of medication reconciliation in the setting of HCV pre-treatment assessment is the opportunity it affords the pharmacist to review patient co-morbidities and co-medications in the setting of hepatic fibrosis and in many cases cirrhosis. Hepatic dysfunction can be problematic when using certain co-medications, which could lead to adverse effects. For example, patients with cirrhosis present using non-steroidal anti-inflammatory drugs (NSAIDs) for pain management. However, NSAIDs can cause kidney dysfunction, reduce the efficacy of diuretics, and increase the risk of upper gastrointestinal haemorrhage, which are all significant concerns in these patients (22).

The pharmacist may also, through identification of an accurate co-medication list, identify strategies to better optimise medication management of co-morbidities. Optimising therapy for underlying disease states (e.g. diabetes mellitus) and general lifestyle interventions including weight loss and reduction or cessation of alcohol, smoking or illicit drug use can also be implemented (22).

The medication reconciliation process also allows the pharmacist to identify if female patients are using contraception. Assessment of both male and female patients for appropriate contraception before initiating HCV treatment regimens that include RBV, a known teratogen with a long half-life, is a key medication safety requirement. If contraception is not in place the clinical pharmacist has the required drug knowledge to make recommendations to the patient and the HCV treating physician (22).

One of the most important aspects of HCV treatment is the fact that it is rarely the exclusive domain of any one type of health care provider. An interprofessional team approach is the best way to ensure optimal treatment results (21). Pharmacist-led medication reconciliation can aid the development of improved and expanded communication between often disjointed healthcare professions. It can promote patient engagement in the active management of their medication which may promote improved medication adherence. Contact with prescribers and patient care providers across the transitions of care is also key with the HCV treatment patient group as they may interact with multiple health care settings, for a variety of co-morbidities, throughout the duration of HCV treatment.

For example, clinical pharmacists play a vital role in the management of HCV in patients transferring from one health care setting to another, for example discharge home post inpatient hospital stay or hospital admission during the course of HCV treatment (168). HCV medications might be inadvertently discontinued or omitted during the hospital transition process. The presence of a clinical pharmacist completing medication reconciliation on admission means that they can ensure therapy continuation and facilitate ongoing DAA supply (168). Better patient understanding of prescribed medication through completion of the process of medication reconciliation also means that the patient is better educated and informed about their medications and more likely to provide information on them to other HCPs they encounter.

Another possible source of problems with HCV treatment is the lack of communication between community and hospital, drug treatment centre or other specialist pharmacies which may dispense HCV therapies (21). Problems can arise when the community pharmacy staff does not have the HCV medications on the patient's medication profile simply because they are unaware of them. Effective communication between community-based and HCV specialist pharmacists is vital to ensure effective screening for DDIs between HCV medications and all co-medications (21). HCV

pharmacists can help to bridge this gap by liaising with each patients' community pharmacy to notifying them about the patient's current HCV medications with the patients' permission (21).

Facilitating medication acquisition is important, especially if hospitalised patients forget to bring in their HCV medications from home. This is crucial, since missed doses of HCV medications, may result in HCV treatment failure and emergence of resistance. HCV medications are costly; therefore, many hospitals do not have these drugs readily available, potentially leading to treatment interruptions. Specialist HCV Clinical pharmacists can assist these practitioners or hospitals by identifying and managing issues associated with HCV medications to ensure successful and safe continuation of HCV treatment (21).

Drug-drug interactions

Since the licensing of the first-generation HCV protease inhibitors in 2011, the pharmaceutical care of HCV has seen an intensity of anti-viral drug development not witnessed since the licensing of highly active antiretroviral therapy for HIV infection in the 1990s. DAAs from three classes, now provide multiple regimen choices for prescribers, all with high rates of SVR (>95%) and good tolerability profiles (61, 68, 207). However, despite the impressive efficacy results reported from clinical trials, real-world experience suggests that approximately 5-10% of chronic HCV patients may fail treatment with current all-oral DAA combinations (121, 207-209). Several factors are postulated to contribute to DAA treatment failure including baseline resistance-associated mutations for DAAs, poor drug adherence and suboptimal DAA regimen selection. Another area of risk which has been reported is the potential for DDIs between HCV DAAs and patient co-medications (210-215). Understanding the DDI potential of new medicines such as DAAs is critical for effective and safe management of HCV. Unidentified or mismanaged DAA DDIs have the potential to lead to patient harm, HCV treatment failure, and development of DAA resistance, which may limit future retreatment options.

First- and second-generation protease inhibitors, telaprevir, boceprevir and simeprevir, while providing a much-needed improvement in SVR rates, possessed significant potential for DDI due to their pathways of metabolism. Both telaprevir and boceprevir are substrates and inhibitors of CYP3A isoenzymes and transport proteins p-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1 and OATP2B1 (22, 216). While the majority of DAAs currently in use (e.g. VEL, G/P, SOF) are considered to have a reduced impact on CYP isoenzymes and P-gp when compared with first generations DAAs, they can still interact with these key transporters. During the phase I clinical trials process, minimal investigational pharmacokinetic studies on DDIs between DAAs and concomitant medicines are undertaken. In addition, clinical trials often exclude complex patient groups including those with multiple co-morbidities, meaning that no information is available on the potential interplay between patient characteristics such as age, liver cirrhosis, presence of co-morbidities or the number of co-prescribed medications on the occurrence, or severity, of potential DDIs. Given the paucity of DDI studies conducted at trial stage, and the resultant limited information available to prescribers on appropriate management of co-prescribed medications in patients with HCV infection preparing for treatment, it is postulated that DDIs are a factor in higher DAA failures rates among real world cohorts (68).

There is a breadth of published literature available assessing the theoretical potential for DDI occurrence with DAAs, confirming that DAAs are still subject to a significant potential for DDIs and that health care practitioners may expect a medication with CYP3A DDI potential in two-thirds of patients with HCV (217-219). A review of co-prescribed medicines among patients with chronic HCV in Europe in 2016 determined that 20% of patients would have at least one contra-indicated DDI with a DAA, if they were to progress to treatment (211). However, only three published data sets from real world patient cohorts reporting the identification and management of DDIs HCV patients as they progress along the treatment pathway were identified during literature review (184, 210, 220).

Data from one real world patient cohort study identified that approximately 66% of patients were at risk of a potentially significant DDI with recently approved DAA regimens (210). In the GRUviC study by Chamorro-de-Vega *et al*, DDI management accounted for 47.8% of pharmacist interventions (184). The acceptance rate of pharmacist interventions by prescribers was high at 99.4% (184). However, it should be noted that details of the specific intervention actions and recommendations made by pharmacists to prescribers are not described in this study. For example, how DDIs were managed and what advice was given in relation to management of specific adverse effects.

Complex patient groups including those with multiple co-morbidities, subject to polypharmacy and liver cirrhosis are identified as having a heightened risk of a DDI. In addition, certain co-medications are frequently cited in DDI scenarios including PPIs, and dihydropyridine derivatives (210). The growing risk of DDIs associated with herbal supplements and multivitamins was highlighted by Langness *et al*, with 36% of patients identified as at risk of a DDI between prescribed DAAs and herbal supplements or vitamins (215).

Studies have also identified the potential for DDIs with anti-retrovirals, which is significant given that one-third of the HIV infected population worldwide are co-infected with HCV (221-224). A UK prevalence study spanning 2008-2014 reported that 5.0% of adults with a current HCV infection also had a diagnosis of HIV co-infection (225). Published research assessing the theoretical potential for DDI occurrence between anti-retrovirals and DAAs is multiple (219, 221, 222). These publications confirm that newer DAAs are still subject to a significant potential for DDIs with multiple anti-retrovirals regimens (226). However real-world studies to date have in the main excluded patients with HIV co-infection (221, 222). HIV/HCV co-infection is linked to more rapid fibrosis progression and associated morbidity and mortality (227, 228). Thus, it is a priority to treat people living with HIV and HCV with DAA therapy (144). In fact, a major limitation of many real-

world DDI studies completed with DAA regimens to date has been the exclusion of patients with HIV co-infection (210, 211). A study by Olea *et al*, describing the role of the pharmacist in the care of HIV/HCV patients treated with DAA therapy gave no detail regarding specific management strategies for DDIs encountered or adverse effects that occurred (144).

Given that approximately one-third of the HCV infected population are co-infected with HIV, there is currently a valid need for real world data on DDI potential in the co-infection setting (227, 228). Availability of data on DDI occurrence with all anti-retroviral regimens and management strategies within real world heterogeneous cohorts will aid HCPs involved in HCV treatment in making better informed decisions regarding DDI assessments.

Knowledge and awareness of DDIs has become a key step in the evaluation of patients starting on and successfully completing HCV combination therapy (216). Pharmacists are uniquely placed to fulfil the role of DDI review. The presence of a pharmacist in the HCV clinic permits real-time checking for DDIs (229). This checking can be done efficiently by the pharmacist at the point of care and immediately discussed with the attending physician, thereby preventing adverse effects or potential treatment disruption (229).

It is clear that a significant number of patients are at risk for DDIs when treated with HCV multi-DAA regimens and that the challenge of DDIs will continue to be part of HCV therapy in the coming years, in particular, as combination treatments with several DAAs will most likely be standard of care for all patients in the future. A greater knowledge of the medication use patterns in a large heterogeneous population would add to our understanding and insight into the potential for interactions with current and emerging HCV agents (217). To date, there have been no studies published describing or measuring the outcome of pharmacist-led interventions as part of HCV anti-viral pre-treatment assessment.

Completion of DDI review is a time intensive process using clinical pharmacist expertise and involves assessing data from multiple sources which is being continually updated. However, this time cost is necessary to ensure delivery of safe and effective HCV therapy. To date no study has been published assessing the time and resource costs of this important patient safety practice in HCV treatment patients.

2.1.2. Method

Study Design & Setting

A retrospective observational cohort study of 300 patients with chronic HCV infection treated with DAAs at two outpatient clinics at St. James Hospital. St. James's Hospital had the first Hepatitis C specific pharmacist service in Ireland.

The retrospective study design was informed by the knowledge of the researcher and from anecdotal reports from pharmacist colleagues that significant numbers of medication reconciliation and drug-drug interaction issues were being identified during the pharmaceutical care process for patients treated for HCV infection at St. James's Hospital. A sample size of 300 was chosen as this represented the number of patients it was estimated by clinicians, that would be treated annually with DAA therapy at clinics in St. James's Hospital.

Study Population

Patients treated with oral HCV DAA therapies at two outpatient clinics at St. James's Hospital (Hepatology and Infectious Diseases) between December 2014 and February 2017 were included in this analysis of the pharmacist-led medication reconciliation and DDI review and management process. Patients were eligible for inclusion if they had medication reconciliation and DDI review completed by an on-site clinical pharmacist which was part of standard practice during the study period (Figure 2.1). Patients were excluded from this study if they were enrolled in a clinical trial

or did not start DAA therapy. Clinical trial participants were excluded as their path through treatment was different to the standard of care in the Hepatitis C treatment service which was being studied. Patients who were proposed for HCV treatment but did not start to take DAA therapy were excluded as monitoring of DDI management and outcome along with treatment outcome data (which were outcomes of this study) would not be available for these patients.

Only patients treated with DAA regimens were included in this study meaning that patients treated with IFN regimens were excluded. The decision to exclude patients receiving IFN based regimens was made based on the fact that as of December 2014, DAA treatment became the preferred treatment option for patients. However, due to national guidelines and the high cost of DAAs, most patients were not initially eligible to receive them. The majority of these patients opted to wait for when DAAs were available to them. Therefore, the IFN treatment cohort represented a small number of patients during the lifetime of this study and was not representative of the general treatment options taken by patients.

Study Objectives

Pharmacist-led medication reconciliation:

- To identify and quantify medications in use by the study population using the process of pharmacist-led medication reconciliation.
- To compare the list of medications identified through pharmacist medication reconciliation with the medication list documented in the patient medical notes and categorise any variances identified.

Analysis of the potential severity of risk associated with medication reconciliation variances

- To obtain peer review of episodes of medication variance identified as part of the pharmacist-led medication reconciliation process with assignment of risk ratings using a validated tool for

scoring the severity of medication errors, the Visual Analogue Scale. This peer review process was undertaken by clinical pharmacists.

Assessment of the potential drug-drug interactions (DDIs) between patient co-medications and direct-acting anti-virals

Primary objectives:

- Assess the prevalence, type, and severity of DDIs between DAAs and identified patient co-medications in the cohort.
- Describe pharmacist-developed DDI management strategies
- Assess the rate of acceptance, among prescribers, of the pharmacist-developed DDI management strategies

Secondary objectives:

- To evaluate the association between baseline patient characteristics and the risk of DAA DDI occurrence
- To evaluate the association between potential DDIs identified as part of pre-treatment pharmacist assessment and attainment of SVR.

Research Ethics Approval

Ethics approval was obtained from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (Appendix 1, 2). REC 2016-05; Chairman's action (11, 12) Date approved: 09/05/2016. During the lifetime of this research project, the 2018 Health Research Regulations came into effect. Data collected as part of this research project was collected in 2017 and patient information collected was fully and irrevocably anonymised in 2017. This project is in compliance with Health Research Regulations.

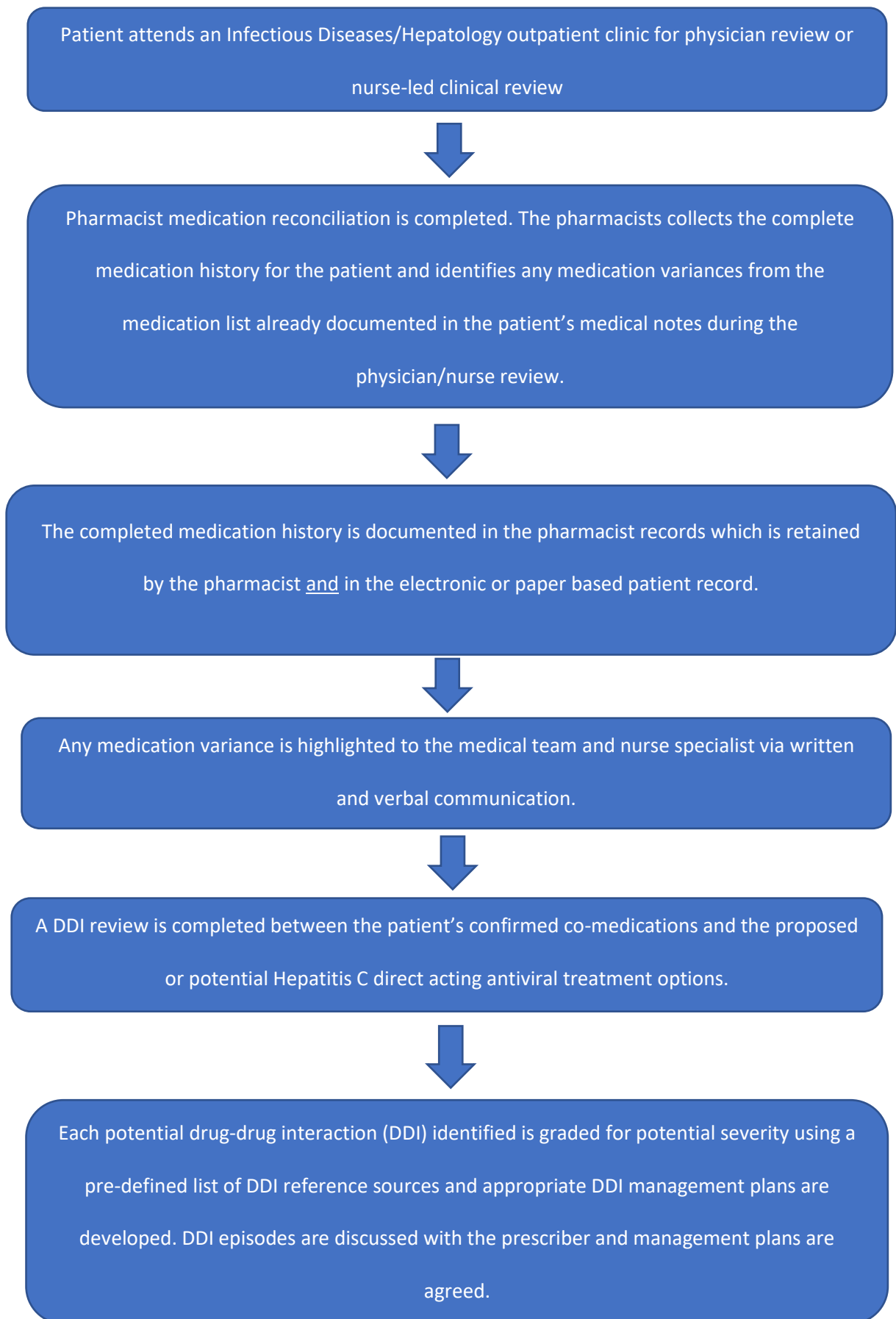


Figure 2.1 Hepatitis C pre-treatment pharmacist assessment process in St. James's Hospital

Study 1: Pharmacist-led medication reconciliation

Pharmacist-led medication reconciliation was completed for all patients included in this study by the lead researcher (Figure 2.1). Medication reconciliation was completed by the research pharmacist. A data collection form was designed to collect information for this study (Appendix 3). Patient variables collected included patient age, gender, presence of cirrhosis, co-morbidities, HCV acquisition risk and allergy status. Information collected in relation to the completion of pharmacist-led medication reconciliation included sources used to complete the process, medication name, dose, frequency and formulation. Potential sources of medication reconciliation included patient interview, community pharmacy records, patient carer interview, drug treatment centre dispensing records, patient medication lists and GPs. The medication reconciliation process aimed to identify all prescription medicines, over the counter (OTC) products, herbal supplements, multivitamins and illicit substances prescribed or in use by each individual patient. Patient co-medications captured during medication reconciliation were classified using the anatomical chemical classification system from the WHO www.whooc.no (230). The Anatomical Therapeutic Chemical (ATC) Classification is an internationally accepted classification system for medicines that was developed and is managed by the World Health Organisation (WHO). It was used in this study as it permits grouping of medications by drug class (e.g. proton pump inhibitors) which aided analysis of patient co-medications. Data was collected retrospectively using several sources including electronic patient medical records, pharmacy medication reconciliation records and paper-based patient medical notes.

The medication list obtained through the medication reconciliation process was compared with the medication list documented in the patient medical notes by the physician or nurse who completed the HCV treatment assessment, to identify any variances. The term variance was used to describe any difference identified between the medication list documented in patient medical notes by the medical team or nurse and that recorded during the pharmacist medication reconciliation process.

Any reconciliation variances identified were classified into five categories; medication omission, medication commission, dose variation, frequency variation and medication formulation variation. Variances identified were communicated to the medical team verbally and in writing. Medication commission refers to the prescribing of medications which were incorrectly thought to be part of a patient's pre-admission medication list.

Study 2: Analysis of the potential severity of risk associated with medication reconciliation variances.

This was a cross sectional observational study. A random sampling method was used to select fifty patients from this overall study cohort of 300 patients treated for HCV infection between December 2014 and February 2017. A random sampling method was chosen to remove any potential bias that may be introduced by the research pharmacist selecting patients for inclusion in this study sample.

The study identifier numbers for all 300 patients recruited in to the medication reconciliation study were entered into a Microsoft Excel® sheet. The RAND function in Microsoft Excel® was used to generate a column of random numbers alongside the column containing the study identifier numbers. The random numbers were then arranged from smallest number to biggest number. The study identifier numbers linked with the fifty lowest random numbers represented the patients selected for inclusion in this sub-study.

A sample size of fifty patients was chosen for this study for a number of reasons. Firstly, the process of reviewing and grading the severity of medication variances by clinical pharmacists was deemed to be a time intensive process for pharmacists participating. Therefore, it was deemed impracticable to complete this sub study with the full 300 patient cohort from the medication reconciliation study.

Given the high rate of medication reconciliation variances identified in the larger study (74% of the 300 patients within the medication reconciliation study were found to have at least one medication variance present) it was decided that a smaller sub-population be randomised to this study. As this study was not measuring the rate of occurrence of medication variances but rather assessing the severity of interventions being identified a sample size of 50 patients was chosen.

For analysis of medication reconciliation variances for this subset of patients, a specific report form allowing variances to be described was designed. (Appendix 4). The report form was completed for each variance identified in this subgroup. The report form provided the reviewer with information including patient age, gender, allergies, co-morbidities, co-medications and a summary of each medication reconciliation variance identified in each case.

Three pharmacists were recruited to complete the process of reviewing and grading the potential severity of the medication variances identified. All three reviewers were provided with a copy of each report form. The Visual Analogue Scale (VAS) (0-10) was used to grade the variances identified, in relation to the potential severity of outcome for patients, if the particular medication variance was not identified prior to initiation of HCV therapy. A guide on how to complete the analysis using the VAS was also provided to each reviewer (Appendix 5) (231, 232). A score of zero would indicate there was no risk associated with the variance identified by the medication reconciliation process. A score of ten would indicate a very severe, potentially fatal risk associated with the variance identified by the medication reconciliation process (Table 2.1). All adverse events identified during the study were communicated to the prescribing physician. Any serious or newly identified potential adverse events were forwarded to the Health Products Regulatory Authority.

Table 2.1 Description of the potential risk (scored using the VAS tool) to a patient due to a variance identified by the medication reconciliation process

Visual Analogue Scale Score	Description of risk to patient
0	No risk associated with the variance identified by the medication reconciliation process
1-3	Minimal risk associated with the variance identified by the medication reconciliation process
4-6	Moderate risk associated with the variance identified by the medication reconciliation process
>7	High or severe risk associated with the variance identified by the medication reconciliation process
10	Severe, potentially fatal risk associated with the variance identified by the medication reconciliation process

Study 3: Drug-drug interactions between DAAs and co-medications

The next pharmacist-led intervention assessed was the process of DDI assessment.

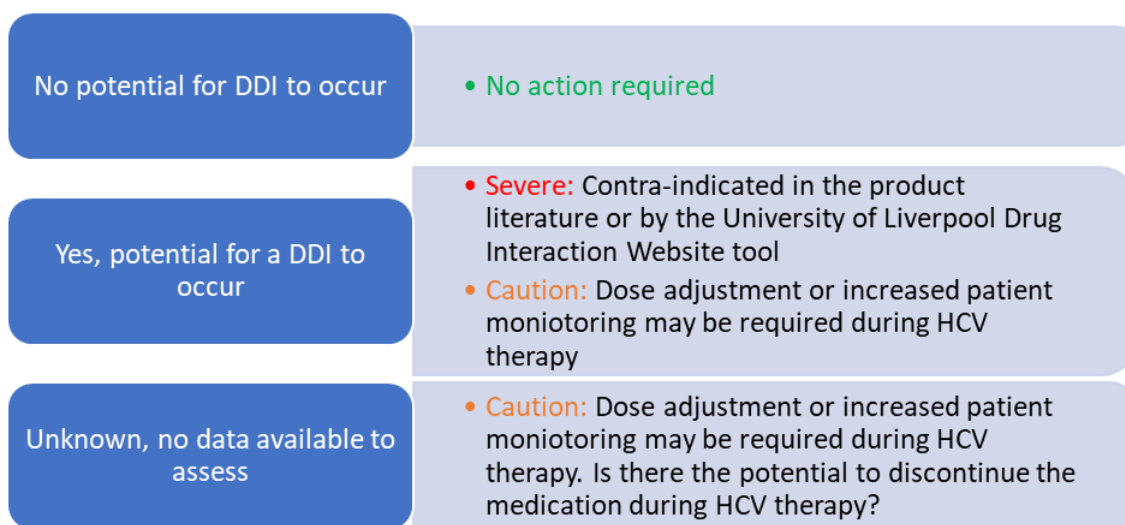
This was an observational cohort study to measure the prevalence, type & severity of DDIs between DAAs and identified patient co-medications. A standardised DDI reference list including the specialised University of Liverpool online resource was employed (233). (Appendix 6). A data collection proforma was designed to collect study data for all 300 patients recruited to this study. (Appendix 7). The study also sought to determine the pharmacist-developed DDI management strategies and to assess the rate of acceptance, among prescribers, of the pharmacist-developed DDI management strategies.

DDI identification and classification

A DDI review was completed between the proposed DAA regimen agents and each co-medication as confirmed by the medication reconciliation process. Where a patient was taking a combination product containing more than one medicine, the medicines were counted as individual medicines for the purpose of DDI assessment. The exception to this was herbal supplements and multivitamin products containing more than six active constituents. These products were considered as one

medicine for the purpose of the analysis as many of these products were multivitamins or supplements where the individual constituents were not available in individual product form. Therefore, if a DDI was identified with any one of the combination product constituents then that particular product was precluded from use during HCV treatment.

DDI outcome assessments resulted in three descriptive categories based on the potential for a DDI to occur: nil interaction found, potential interaction identified or potential for DDI unknown. (Figure 2.2) When a potential interaction was identified a clinical significance rating was applied (Nil DDI; Mild DDI; Moderate DDI; Severe DDI). DDI significance ratings applied were based on classification systems in use by established DDI reference sources (233-235). When the potential for interaction between DAA therapy and a co-medication was unknown, a review of co-medication indication was completed.



DDI: Drug-drug interaction; HCV: Hepatitis C

Figure 2.2 DDI Assessment & Classification

DDI Management

Where a potential interaction was identified, six DDI management recommendations were incorporated into the pre-treatment pharmacist assessment DDI review to guide patient care

(Figure 2.3). The type of DDI management recommendation chosen for each DDI identified in this study was driven by the clinical significance rating applied to the DDI, the indication for the co-medication and the alternative treatment options that were available for that specific co-morbidity for that specific patient. Management recommendations were communicated to the medical team and nurse specialist verbally and in writing. DDI management strategies were adhered to from commencement to completion of DAA treatment, at which point they were reviewed.

1. Discontinuation of an interacting medication during Hepatitis C therapy
2. Dose adjustment of an interacting co-medication
3. A change in the interacting medication to an alternative in class or in clinical effect
4. Initiation of a monitoring plan
5. A dose time separation strategy
6. Consideration of an alternative Hepatitis C treatment regimen

Figure 2.3 DDI management recommendations developed for this study

Statistical Analysis

Study 1, 2 & 3: A Microsoft Excel® database was designed to collate, code (anonymise) and analyse the study data. Statistical analyses of the study findings were performed using IBM SPSS (version 24.0) with significance levels set at $P \leq 0.05$.

Study 1 & 2: Descriptive statistics were used to present the data. Data collected as part of the study was both categorical and continuous. Relative risk analysis was completed to assess the degree of association between specific patient characteristics and medication variance identification during the medication reconciliation process. Within the medication reconciliation variance assessment study, inter-rater variability was calculated to measure the degree to which different reviewers agreed on the estimates of risk they associated with specific variance episodes.

Study 3: Descriptive statistics were used to describe study cohort demographics. Odds ratios (OR) were calculated to assess the level of association between the baseline characteristics of study patients and the risk of DAA DDI occurrence. HCV DAA regimens were analysed using this method to assess if any DAAs were associated with an increased DDI potential. Calculation of odds ratios, which are a direct measure of association, allowed the tools of multiple regression to be applied to frequency data to analyse the influence of several patient factors on the risk of DDI occurrence. The impact of DDI occurrence on SVR rates was also assessed.

The odds ratio is the ratio of odds of a DDI occurring in one group with a specific characteristic present versus the odds of a DDI occurring in another group where that risk factor (e.g. HIV co-infection is absent). In comparison the relative risk analysis method is a ratio of the risk of an event in one group versus another. It should be noted that when a particular outcome is rare (<10% occurrence in a study population), the value of the odds ratio is not too different from that of relative risk.

*Note for Study 3 analysis: RBV was co-prescribed in 76% of study cohort. Given that cytochrome P450 (CYP450) isoenzymes and hepatic transporters are not involved in the metabolism of RBV, it does not participate in a significant number of DDIs. For this reason, RBV was excluded from analysis in this study.

Data management

Data collected as part of studies 1-3 were entered onto a password encrypted Microsoft Excel® database. Data entry onto the database occurred on site at St. James's Hospital using a computer accessible only to staff within the pharmacy department via individual log on details. The database passwords were available to two people, the primary investigator and an appointed other. A codebook was written for the study database. Patient data was fully and irrevocably anonymised.

The excel database once complete were transferred to SPSS® in a coded format for statistical analysis.

2.1.3. Results

A total of 300 patients were included in this study of whom 71% (N = 213) were male (Table 3.2). The average age of the study population was 50 ± 10.6 years. The average number of co-morbidities among patients in the study cohort was four. Common co-morbidities included gastro-intestinal conditions and depression (Table 2.2). Patients with more than six co-morbidities accounted for 11.7% of the cohort.

Table 2.2 Baseline characteristics of the study cohort

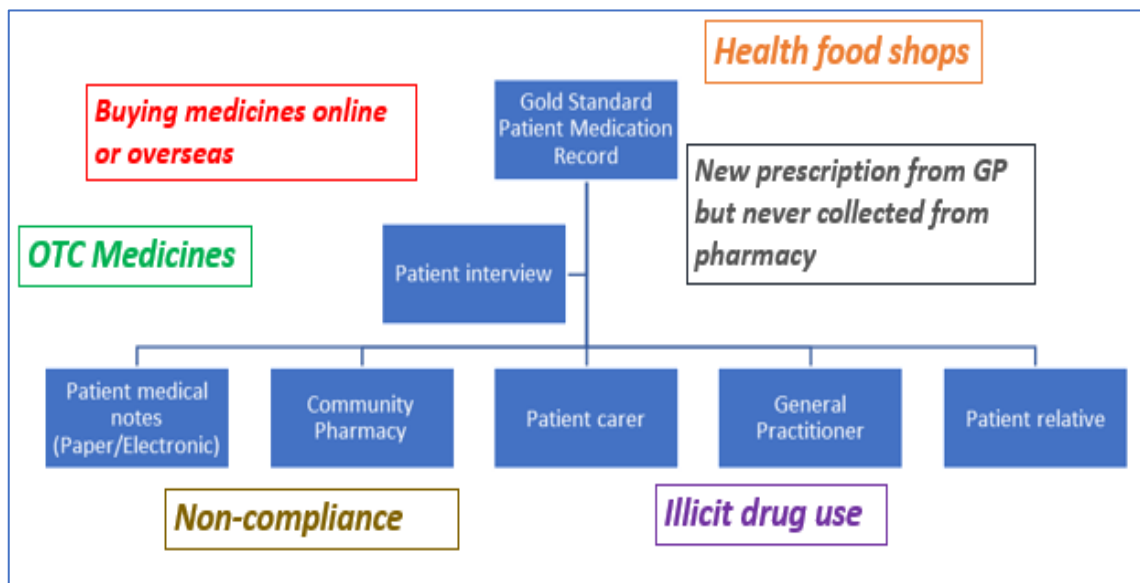
	N = 300
Age at time of review (mean \pm SD) (Range), years	50 years \pm 10.6 (25-81)
Male, n (%)	214 (71.3)
Presence of cirrhosis, n (%)	188 (62.7)
Route of acquisition, n (%)	
PWID	180 (60)
Sexual transmission	14 (4.67)
Infected blood products	71 (23.7)
Vertical transmission	1 (0.33)
Unknown risk	20 (6.67)
Origin from country of high prevalence	11 (3.67)
No. of co-morbidities (Mean \pm SD (Range))	3.5 \pm 2.21 (0-11)
Types of co-morbidities, n (%)	
Gastro-intestinal conditions	112 (37.33)
Depression/ Anxiety	84 (28)
HIV Co-infection	70 (23.3)
Respiratory conditions	65 (21.67)
Cardiovascular disease	61 (20.3)
Chronic pain	45 (15)
Dermatological conditions	29 (9.7)
Diabetes mellitus	22 (7.33)
Epilepsy	13 (4.3)
Malignancy	12 (4)
HCV Genotype (G), n (%)	G1 ⁺ : 207 (69) G2: 3 (1) G3: 74 (24.7) G4: 12 (4) Mixed genotype: 4 (1.3)

SD: Standard deviation; PWID: People who inject drugs; HIV: Human immunodeficiency virus; G: Genotype; HCV: Hepatitis C

Study 1: Medication reconciliation

Process of medication reconciliation

The three most commonly used information sources for completion of medication reconciliation were patient interview (94%, N =282), electronic patient records (74%, N = 222) and the patient medical notes (68%, N = 204) (Figure 2.4). Among the study population, 88% (N = 264 patients) were taking at least one medication at baseline. The medication reconciliation process identified 1543 co-medications, including both prescribed and non-prescription (Appendix 23). Patients taking more than three co-medications accounted for 67.6% (N = 203 patients) of the study population. The average number of co-medications per patients within the study group was 5 (5± 4.6 (Range 0-27)). The average time taken to complete the process of medication reconciliation per patient was 19 minutes (Range 1 minute – 53 minutes). Figure 3.4 highlights some of the wide range of medication reconciliation sources (in blue) utilised during this study.



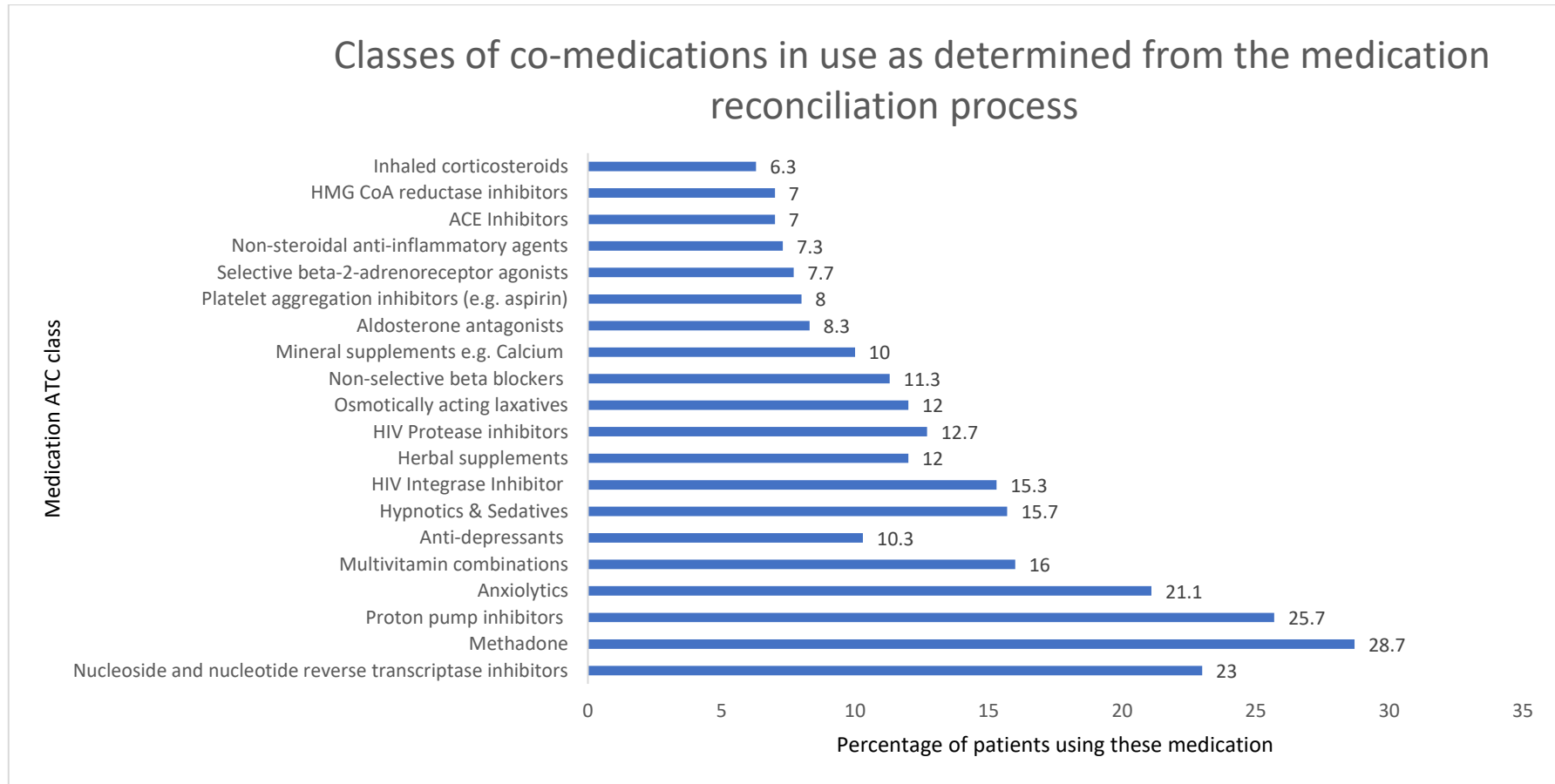
OTC: Over the counter; GP: General practitioner

Figure 2.4 Medication and information sources to be considered as part of the medication reconciliation process.

Types of co-medications identified

Co-medications most frequently identified during the pharmacist-led medication reconciliation process included proton pump inhibitors (PPIs)/H2 receptor antagonists (27.6%, N = 83), methadone (28.7%, N = 86), benzodiazepines (21.7%, N = 65) and anti-retrovirals (23%, N = 70) (Figure 2.5, Appendix 23). Significant usage of multivitamin (16%, N = 48) and mineral supplements (10%, N = 30) was identified, accounting for 9.5% of total co-medications. Usage of other CAM products was identified in 12% (N = 36) of the patient population. Examples of products in use included milk thistle, concentrated green tea formulations and valerian. It was decided to further investigate this trend of complementary and alternative medicine use via a patient questionnaire in a separate study following the initial medication reconciliation study.

Classes of co-medication in use as determined from the medication reconciliation process



Abbreviations: ACE: Angiotensin converting enzyme; HMG: hydroxymethylglutaryl; HIV: human immunodeficiency virus

Figure 2.5 ATC Classification of co-medication in use as determined from the medication reconciliation process

Medication Variances

The term variance was used to describe any difference identified between the medication list documented in patient medical notes by the medical team or nurse and that recorded during the pharmacist medication reconciliation process. Medication reconciliation identified episodes of medication variances affecting 74% (N = 222) of the study population with medication omission occurring most frequently (87%, N = 588 episodes). Other variances identified included omission of medication dosage information (7%, N = 41), medication dose variance (5%, N = 30) and omission of medication dosage frequency (1%, N = 7).

Study 2: Analysis of medication reconciliation variances

A total of 50 patients were included in this sub-analysis of whom 43 were male. (Table 2.3) Common co-morbidities among the study population included addiction (44%), HIV (32%) and liver cirrhosis (34%) which mirrored the overall study cohort.

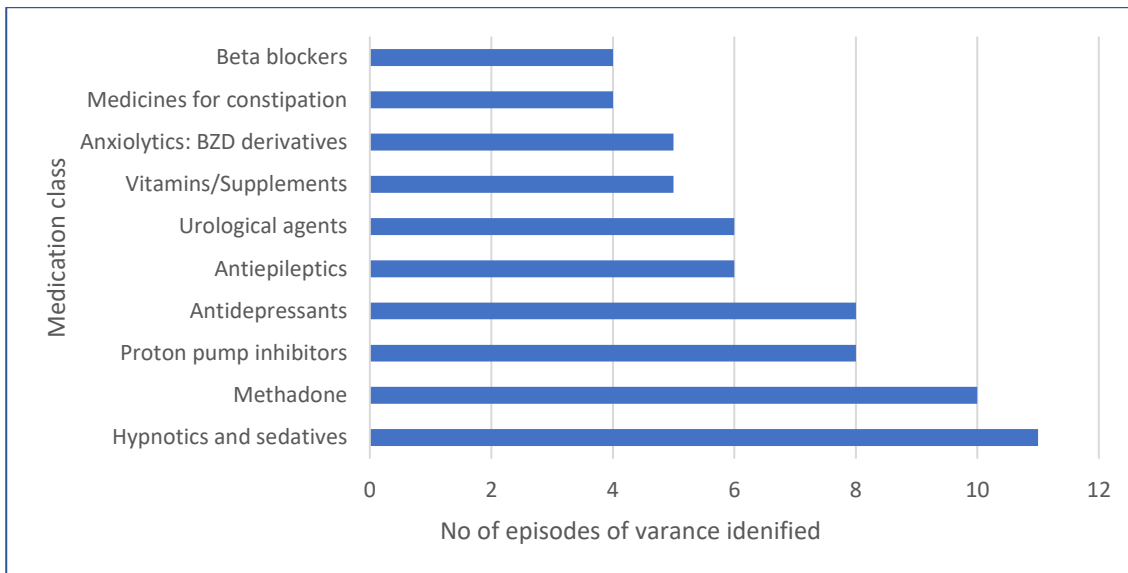
Table 2.3 Patient characteristics

	N = 50
Age at time of review (mean \pm SD) (Range), years	42.5 years \pm 8.6 (26-65)
Male, n (%)	43 (86)
No of co-morbidities (Mean (Range))	3.5 (1-8)
No of concurrent medication (Mean (Range))	3 (0-17)

SD: Standard deviation

Medication variances

The medication reconciliation process identified 163 medications among the sub-study population. A total of 98 medication variances were identified affecting 74% of this sub-study population. Allergy status was not recorded in 46% of patient cases. Non-prescription medications including vitamin and mineral supplements and other CAM products accounted for 9.1% (13) of all medication variances identified. Medications most frequently involved in medication variances episodes included hypnotics and sedatives, methadone, PPIs and anti-depressants. (Figure 2.6) A medication variance episode refers to each individually identified medication variance. Therefore, one patient may have multiple medication variance episodes.



BZD: Benzodiazepines

Figure 2.6 Medication types most commonly involved in episodes of medication variance

Relative risk analysis identified patients with HIV co-infection, liver cirrhosis and those prescribed three or more co-medications as being at a statistically significant increased risk of medication variances in the outpatient setting (highlighted in bold text in Table 2.4).

Table 2.4 Relative risk of medication variance occurrence based on specific patient characteristics

Patient Characteristic	Relative Risk	Confidence Interval 95% (Lower-upper)	P-value
Age >50 years	0.9491	0.5011- 1.7974	0.8726
Presence of cirrhosis	1.5772	1.0162- 2.4497	0.0422
HIV co-infection	1.7266	1.263- 2.6468	0.0122
≥ 3 Co-meds	2.25	1.3332- 3.7972	0.0024
≥ 3 morbidities	1.7922	0.9629- 3.3359	0.0657

*Numbers in bold are statistically significant.

Medication Variance Severity

A median visual analogue score of ≥ 7 was assigned to 16 medication variance episodes (16.3% of the total number of variances identified). This is indicative of a high risk of potential harm to the patient. Medications used in the treatment of epilepsy accounted for four high risk variances. (Table 2.5)

Table 2.5 Highest VAS scores relating to episodes of medication variance identified.

Medication variance episode	Visual analogue scale score assigned by pharmacists (Median)
Carbamazepine 400mg four times daily: Not documented.	9
Methadone 105mg once daily: Not documented.	8
Methadone 100mg once daily: Not documented.	8
Oxycodone prolonged release twice daily: Not documented	8
Olanzapine 10mg twice daily: Not documented	8
Mirtazapine 45mg at night: Not documented	8
Levetiracetam 750mg twice daily: Not documented	8
Methadone 45mg once daily: Not documented	8
Levetiracetam 1.25mg in the morning: Not documented	8
Levetiracetam 1g at night: Not documented	8

Inter-rater reliability (IRR) among the three pharmacists who completed the variance assessment was calculated as 69% which is indicative of a good level of consistency and agreement among peer review severity scores. However, it should be noted that due to the small number of reviewers and the fact that all three were clinical pharmacists, a good level of consistency of scoring would be expected. The small number of peer reviewers and the fact that all reviewers were from one healthcare profession in some way limits these results.

Study 3: Drug-drug interactions between DAAs and co-medications

Initial choice of HCV DAA treatment

Available licensed DAAs during the study time period were SOF, LDV, DCV, P/rOD (Table 2.6). It should be noted that for the first five months of the study period, DAA access was limited to SOF/LDV. For the remainder of the study period there was no restriction of DAA regimen choice by the prescriber.

Table 2.6 Initial choice of HCV treatment

Direct acting antiviral (DAA) regimen	Patients prescribed this regimen as initial DAA treatment option (%) †
	N = 300
Sofosbuvir/ledipasvir (SOF/LDV) ‡	160 (53.3%)
Sofosbuvir/daclatasvir (SOF/DCV) ‡	72 (24%)
Paritaprevir/ritonavir/ombitasvir/dasabuvir (P/rOD) ‡	67 (22.3%)
Sofosbuvir/ribavirin (SOF/RBV) ‡	1 (0.33%)

† For the first five months of the study period DAA access was limited to SOF/LDV. For the remainder of the study period there was no restriction of DAA regimen choice by the prescriber.

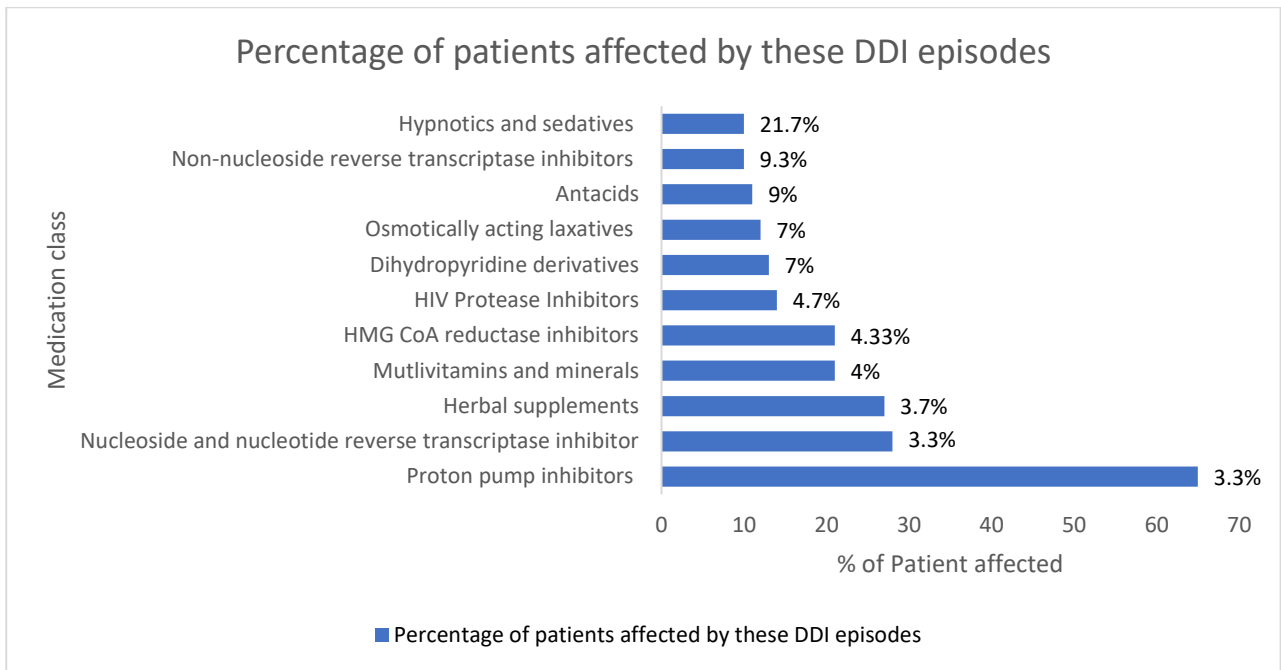
‡ These commonly used and accepted abbreviations for DAA regimens will be utilised throughout this article.

Drug-drug interaction assessment

From a total of 1543 concomitant medicines identified, 477 potential DDIs with DAAs were identified, involving 160 different co-medications and affecting 71% (N = 187) of patients taking medicines. This corresponds to an average of 1.59 DDIs per patient. The number of potential DDI episodes identified in a single patient case ranged from 1 -18. Three or more potential DDI episodes were identified in 13.7% of patients. Prescription and OTC medications accounted for 85.1% (N = 406 episodes) and 4.8% (N = 23 episodes) of potential DDI episodes respectively. The medications

most commonly associated with any severity level of potential DDI with DAAs were PPIs 22% (N = 65 episodes) (Figure 2.7). The majority of these interactions were related to co-prescription of ledipasvir (NS5A inhibitor) with PPIs (86%). Similarly, all interaction episodes identified with antacids and H₂ receptor antagonists were associated with the SOF/LDV regimen. Among the OTC medications linked with potential for DDI occurrence were four episodes involving PPIs purchased as OTC products. Complementary and alternative medicine products and vitamin products accounted for 5.7% (N = 27) and 4.4% (N = 21) of potential DDI episodes respectively. No emerging trend was identified between herbal supplements, multivitamins and DDIs with specific DAA regimens.

Potential boosting of tenofovir drug levels when co-administered with SOF/LDV affected 9.3% of the total patient population, which encompasses 40% of the HIV co-infected cohort. DDI episodes involving HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) were most common with the SOF/DCV regimen. This DAA regimen was involved in 57% of NNRTI DDI episodes. Interactions between statin therapy and dihydropyridine derivatives and DAA regimens were identified in 34 patients (11.3% of patients), with SOF/LDV and P/rOD responsible for 91% of these potential DDIs. The P/rOD regimen was implicated in all DDIs identified with co-prescribed sedatives and hypnotics.



Abbreviations: HMG: hydroxymethylglutaryl; HIV: human immunodeficiency virus

Figure 2.7 Co-medication classes found to be most frequently at risk of DDI with DAAs and the number (and %) of patients affected in this study.

Association between patient characteristics and DDI occurrence

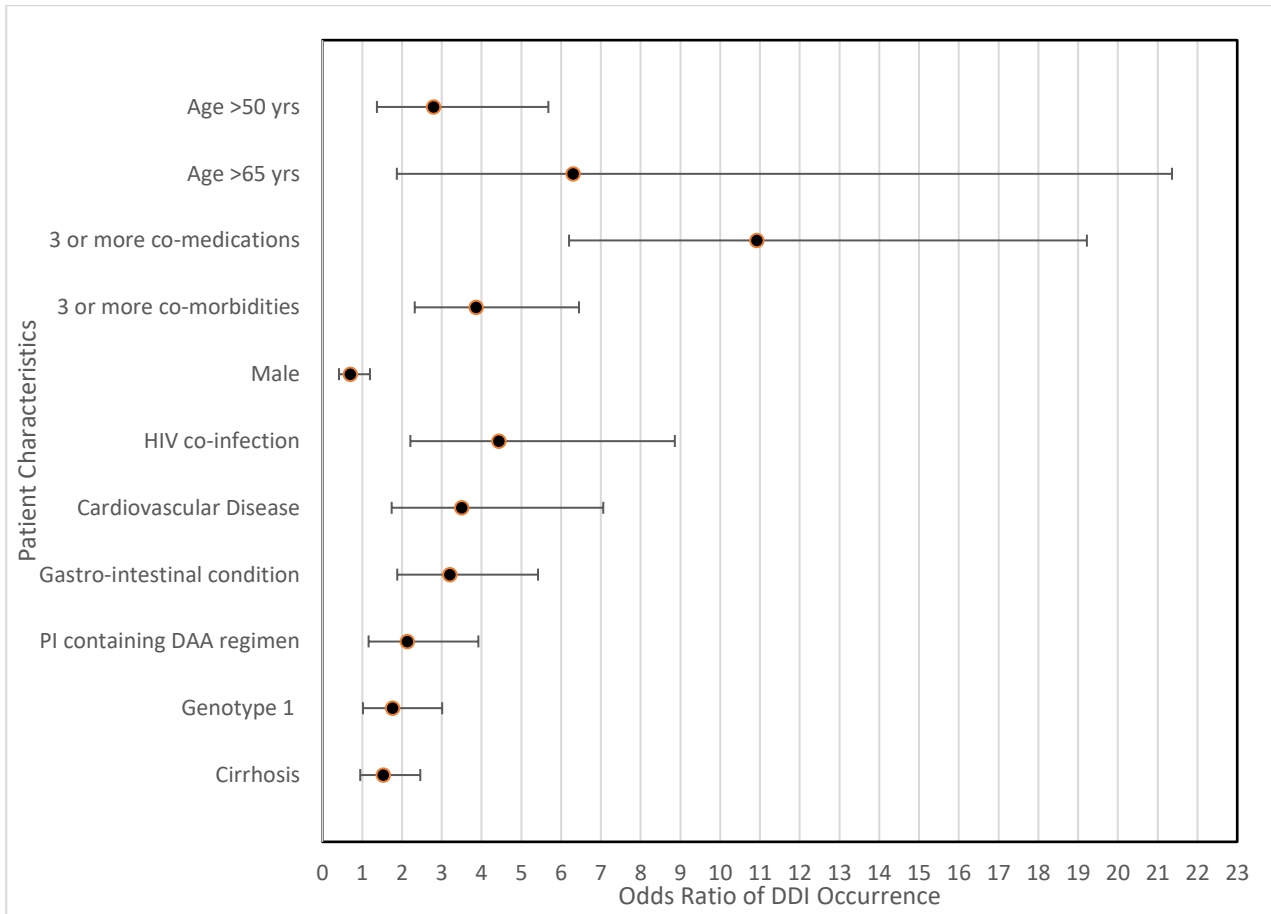
Associations between the baseline characteristics of the patient population and potential for a DDI were identified. The most significant patient factor associated with DDI occurrence was the number of co-medications taken by the patient (>3 co-medications OR 10.92 [CI 95%: 6.2, 19.22; p: <0.05]). (Figure 2.8, Table 2.7). Other factors associated with DDI occurrence included patient age and specific co-morbidities including cardiovascular disease, HIV co-infection and presence of cirrhosis. (Figure 2.8, Table 2.7).

Table 2.7 Odds of an association between patient characteristics and DDI occurrence

Factors	Odds Ratio (OR)	95% Confidence Interval
Age >50 years	2.79	(1.37, 5.68)
Age >65 years	6.3	(1.87, 21.36)
3 or more co-medications	10.92	(6.2, 19.22)
3 or more co-morbidities	3.86	(2.32, 6.45)
Male	0.7	(0.416, 1.19)
HIV co-infection	4.43	(2.21, 8.86)
Cardiovascular Disease	3.5	(1.74, 7.06)
Gastro-intestinal condition	3.2	(1.88, 5.42)
Protease inhibitor based DAA regimen	2.13	(1.16, 3.92)
Genotype 1	1.76	(1.02, 3.01)
Cirrhosis	1.53	(0.95, 2.46)

DAA:

Direct acting antiviral; HIV: Human immunodeficiency virus



HIV: Human immunodeficiency virus; PI: protease inhibitor; DAA: Direct acting antiviral; DDI: Drug-drug interaction

Figure 2.8 Odds of an association between patient characteristics and DDI occurrence

Patient age

Patients older than the average age of the study population (50 years) were found to be almost three times more likely to be subject to a DDI as compared with those aged less than 50 years. (OR 2.79, 95%CI 1.37, 5.68) For patient over the age of 65 years the risk of DDI appears to double again making them six times more likely to be subject to a potential DDI (Figures 2.8, Table 2.7). However, it should be noted there is a wide confidence interval around the odds ratio analysis for the association of DDIs with DAA use in patients > 65 years. Given the relatively large sample size of this study this wide confidence interval implies that there is significant variability among the study population (in patients > 65 yrs) in terms of DDIs identified. Further analysis with a larger cohort of patients within this age range would be needed to get more definite results around the level of risk of DDIs in patients >65 years.

Co-medications:

The odds of DDI occurrence was found to be almost eleven times higher in patients taking three or more medications (67.7% of study population) at the treatment assessment phase. (OR 10.92, 95%CI 6.2, 19.22). (Figures 2.8, Table 2.7) Figure 2.9 appears to show that while risk of DDI occurrence increases in a linear pattern with age, this does not necessarily correlate with the number of co-medications a patient is taking. Rather, the number of co-medications per patient appears to spike when patients enter their 5th and 7th decades. However, patients in their fifties and seventies appear to have a reduction in medication usage. Given the limited number of patients within the higher age bracket of >60 years further analysis of a bigger cohort of such patients may be needed to tease out the meaning of this result.

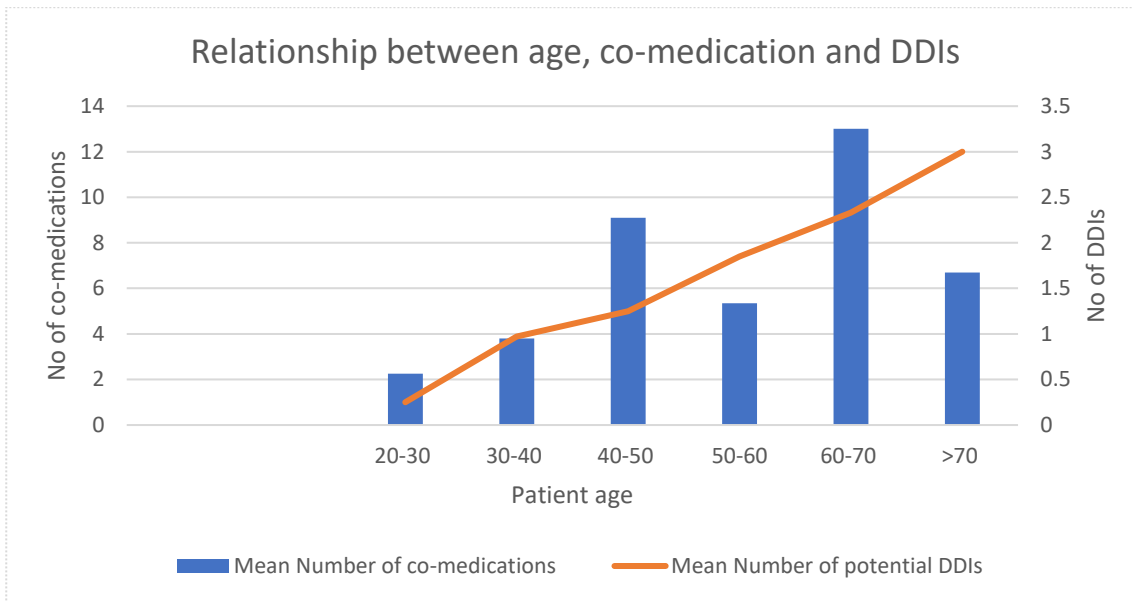


Figure 2.9 Relationship between age, number of co-medications and the potential for DDI

Co-morbidities:

Statistical analysis identified that patients with greater than three co-morbidities at treatment baseline were 3.8 times more likely to be at risk of DDI occurrence. (OR 3.86, 95%CI 2.32, 6.45). (Figures 2.8, Table 2.7). In contrast to figure 2.9, figure 2.10 highlights that the mean number of co-morbidities appears to increase in a linear fashion as patient’s age increases as does the rate of DDI occurrence with HCV DAAs. This tells us that as patients age and have an increasing number of co-morbidities, clinical pharmacists must be vigilant for increased risk of DDIs. The risk of DDIs in older patients does not appear to be down to just co-medication number but rather is influenced by number of co-morbidities present.

Specific co-morbidities:

The odds of a potential DDI were found to be 4.43 times higher in patients with HIV co-infection, 3.5 times higher in cardiovascular disease cases (OR 3.5, 95%CI 1.74, 7.06) and the presence of gastrointestinal conditions increased the risk of DDI occurrence threefold. (OR 3.2, 95%CI 1.88, 5.42). Cirrhosis was not found to be associated with an increased risk of DDI occurrence.

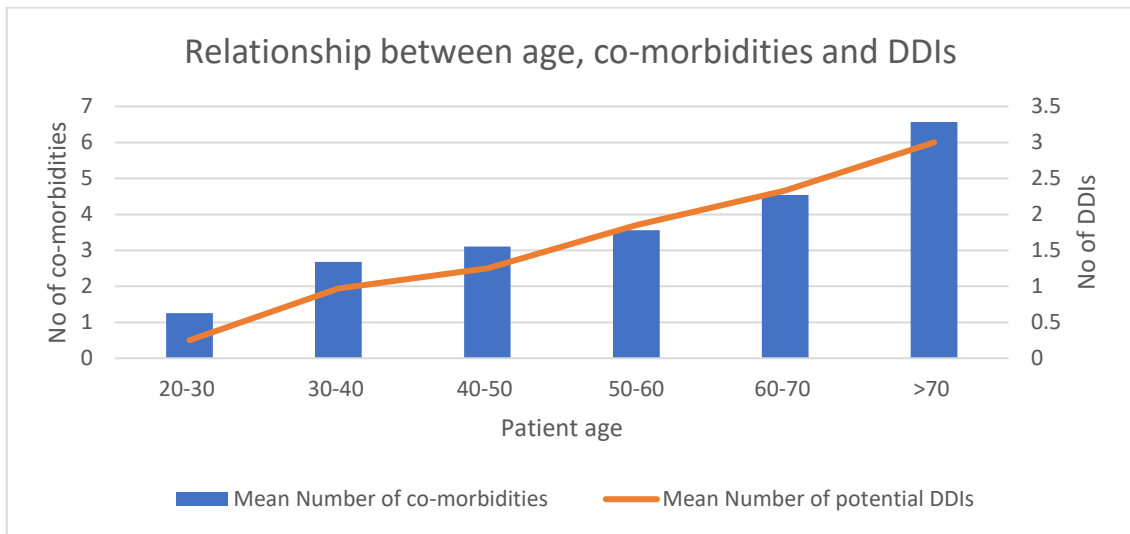


Figure 2.10 Relationship between age, number of co-morbidities and the potential for DDI

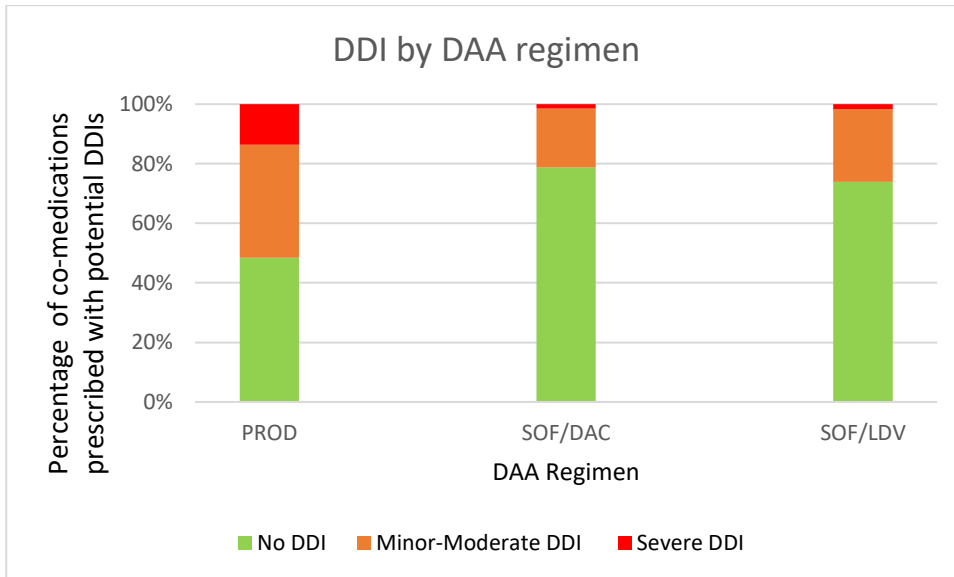
HIV Co-infection:

A total of 182 potential DDIs were identified in this patient cohort. Antiretrovirals accounted for 67 potential DDI cases affecting 71% of the study cohort (50/70).

Association between HCV genotype and DDI occurrence

An association with increased DDI risk was identified for genotype 1 HCV infection with this patient subgroup nearly twice as likely to be subject to a potential DDI. This increased risk of DDI occurrence in genotype 1 patients is driven by the use of protease inhibitors as part of genotype 1 treatment regimens. DAA regimens containing a protease inhibitor were found to be twice as likely to be associated with a DDI as opposed to non-PI containing regimens. (OR 2.13, 95%CI 1.16, 3.92).

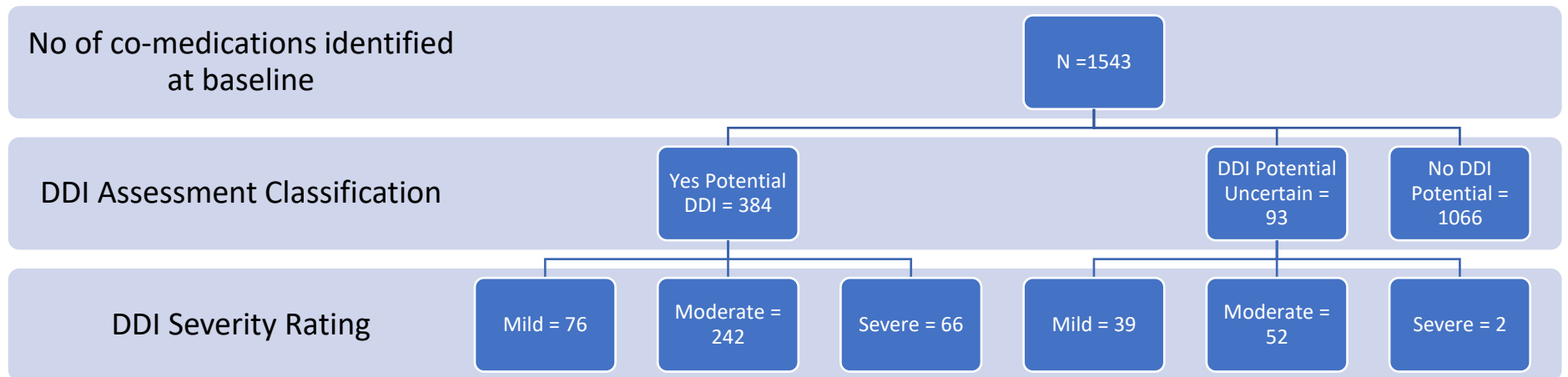
(Table 2.7, Figure 2.9, 2.11)



DDI: Drug-drug interaction; PROD: Paritaprevir, ritonavir, ombitasvir and dasabuvir; SOF/DAC: Sofosbuvir/daclatasvir; SOF/LDV: Sofosbuvir/ledipasvir; DAA: Direct acting antiviral

Figure 2.11 Potential for DDI identified with individual DAA regimens

Classification of DDI severity



DDI: Drug-drug interaction

Figure 2.12 Assessment of the potential for and severity of DDIs with DAAs

A rating of mild was assigned to 115 (24.1%) potential DDIs identified (Figure 2.12). For example, levothyroxine exposure may be increased due to UDP-glucuronosyltransferase (UGT) 1A1 inhibition by the P/rOD regimen which could lead to increased risk of side effects including tachycardia and nausea. This interaction potential was managed by monitoring symptoms and the patient's thyroid stimulating hormone levels during DAA therapy and adjusting the levothyroxine dosage where necessary. There is the potential that the absorption of medicinal products including DAAs could be reduced when co-administered with macrogol products for constipation. Therefore, dose separation should be considered for HCV DAAs and macrogol products. Management strategies utilised for mild DDI episodes included introduction of monitoring plans and separation of dosage times.

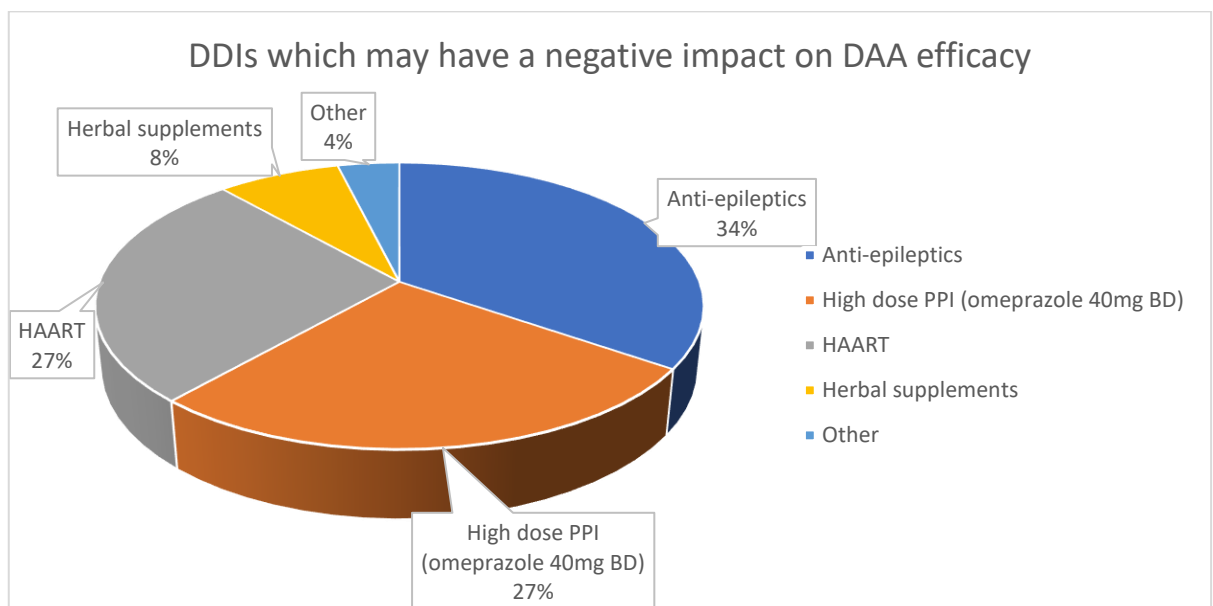
A rating of moderate was applied to 294 (61.6%) DDI episodes (Figure 2.12). DDI episodes classified as moderate required a broader range of management approaches. For example, co-prescription of oxybutynin with P/rOD has the potential to increase oxybutynin adverse effects (including urinary retention and blurred vision) due to the inhibition of the CYP 3A4 isoenzyme by ritonavir. Oxybutynin dose reduction was required in the case of two patients within the study population. Amlodipine exhibits the potential to interact with both SOF/LDV and P/rOD leading to an increase in amlodipine exposure and therefore dose adjustment of amlodipine, particularly for patients prescribed higher dosages, was implemented.

A rating of severe was applied to 68 DDI episodes involving 28 co-prescribed medications and affecting 14.3% of the total study population (Figure 2.12). Of these, 27 DDI episodes affecting 7.5% of patients (N = 22) were identified as having the potential to reduce DAA efficacy, and thus potentially negatively impact HCV treatment outcome. The most common causative medicines for severe DDIs affecting DAA exposure were certain AEDs (41%), all PPIs (36.6%) and specific antiretrovirals (22.7%). Examples included oxcarbazepine, lansoprazole, etravirine, phenytoin, nevirapine and phenobarbital (Table 2.8, Figure 2.13). Co-administration of oxcarbazepine is

contra-indicated with all available DAA regimens due to induction of drug transporter P-gp and CYP3A4 which may lead to a loss of efficacy of the DAA regimen and the potential for emergence of DAA resistance. Therefore, for HCV treatment to proceed, the patient's epilepsy treatment regimen was changed (236).

Table 2.8 Examples of specific co-mediations which may impact on DAA efficacy due to DDIs

Oxcarbazepine	Phenytoin
Lansoprazole	Phenobarbital
Etravirine	Nevirapine

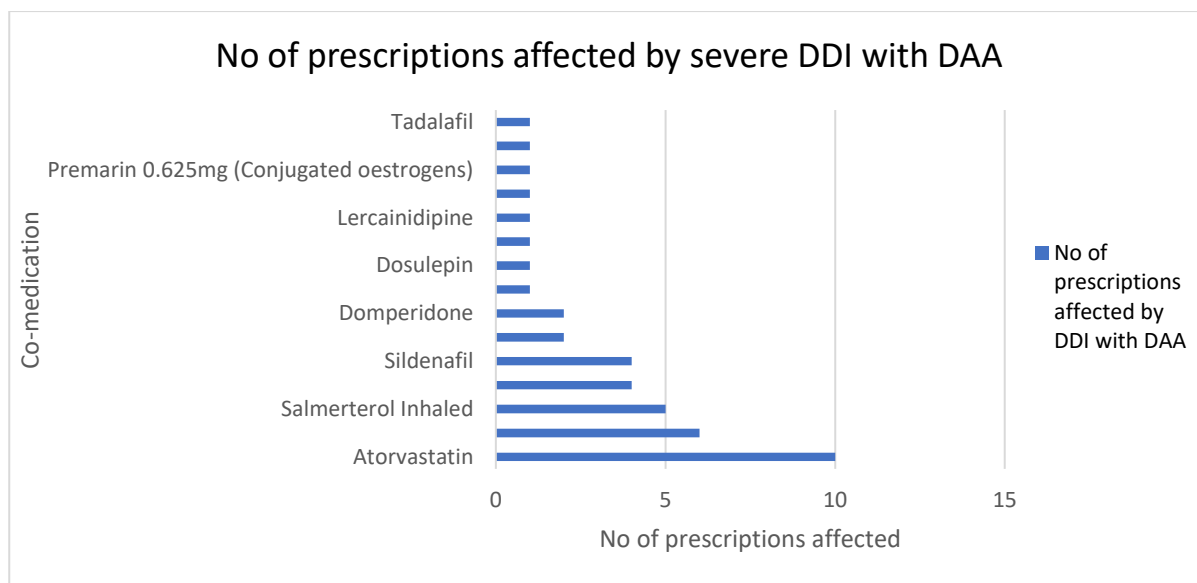


HAART: Highly active antiretroviral therapy; PPI: Proton pump inhibitor; DDI: Drug-drug interaction; DAA: Direct acting antiviral

Figure 2.13 DDIs which may have a negative impact on DAA efficacy in this study cohort

A total of 41 severe DDI episodes which had the potential to negatively impact the efficacy and safety of co-mediations were identified among 6.8% of patients. Examples of co-mediations involved in these severe DDI episodes include inhaled fluticasone and salmeterol, lercanidipine, quetiapine, tadalafil and atorvastatin (Figure 2.14). One example was that of inhaled fluticasone and the DAA regimen, P/rOD. The ritonavir component of this regimen has the potential to cause a significant increase in fluticasone exposure due to inhibition of CYP3A4 isoenzymes which may

cause Cushing’s syndrome and adrenal suppression. One out of three patients with a history of cardiovascular disease and one in eight HIV co-infected patients were found to be at risk of a severe DDI. The P/rOD regimen was most commonly implicated DAA regimen in severe DDIs (72% of severe DDI episodes). The DAA regimen associated with the least potential to be involved in a severe DDI was SOF/DCV.



DDI: Drug-drug interaction; DAA: Direct acting antiviral

Figure 2.14 Number of co-medication prescriptions affected by potentially severe DDIs

DDI Management Strategies

As part of the HCV pre-treatment pharmacist assessment, all potential DDIs identified were linked with an appropriate management strategy. Six specific management strategies were defined within this study (Table 2.9). The most commonly utilised management strategy was initiation of a monitoring plan (36.2%, N = 173 episodes). Temporary medication discontinuation was required in 25% (N = 90 DDI episodes) of the study population. The majority of these cases of medication discontinuation involved herbal supplements and multivitamins (54.3%, N =49) for which limited or no interaction data was available (Table 2.9). Other medications held during DAA therapy included, co-prescribed PPIs (13.3%) and statin therapies (12.2%) based on review of patient characteristics.

Medication dose adjustments were required in 56 patients. Medications requiring dose adjustments included PPIs (55%), statins (10%) and anti-hypertensives (10%) and medications for management of urinary frequency (6.7%). Pre-treatment co-medications were changed to alternatives in 61 DDI episodes to avoid anticipated DDIs. The most common patient groups requiring co-medication changes prior to initiation of HCV DAA therapy (15.1%, N = 72 episodes) were patients with HIV (52.8%, N = 38 episodes) or epilepsy (15.3%, N =11 episodes) and patients with asthma or chronic obstructive pulmonary disease (COPD) who require changes to co-formulated inhalers containing corticosteroids and long acting B₂ agonists (13.9%, N = 10 cases). Dosage adjustments of co-medications and dose time separation strategies were recommended in 60 (12.6%) episodes and 72 (15.1%) episodes respectively. A change in planned HCV DAA regimen was required for eight patients due to severe unavoidable DDIs with anti-epileptic medications and antiretroviral therapy (236). This study data represents the first published study to date which has described the complex nature of DAA DDIs in the epilepsy patient group (236). Table 2.10 illustrates the medication classes most commonly involved in DDIs with DAAs and the recommended monitoring plans.

Table 2.9 Potential DDI Management Strategies

Potential DDI Management Strategy	Number of DDI episodes
Discontinuation of an interacting medication during HCV therapy	90 episodes affecting 52 patients
Dose adjustment of an interacting co-medication	60 episodes affecting 52 patients
A change in the interacting medication to an alternative in class or in clinical effect	72 episodes affecting 51 patients
Initiation of a monitoring plan	173 episodes affecting 98 patients
A dose time separation strategy	72 episodes affecting 50 patients
Consideration of an alternative HCV treatment regimen	10 episodes affecting 8 patients

Table 2.10 Most common medications involved in DDIs with DAAs and monitoring plans/recommendations used.

Concomitant Medication	No. of interaction episodes	Examples of monitoring plans
Antiretroviral therapy	47	Monitor renal function when TDF [†] co-prescribed with SOF/LDV
PPIs	16	Ensure patient is taking PPI simultaneously with SOF/LDV
Anxiolytics	14	Monitor diazepam dosing schedule when co-prescribed with PROD
Antipsychotics	11	Monitor patients for increased morning sedation when mirtazapine and P/rOD co-prescribed
Calcium channel blockers	10	Monitor BP [‡] & HR [§] when amlodipine co-prescribed with SOF/LDV or P/rOD
Hypnotics & sedatives	10	Ensure lowest suitable dose of zopiclone is prescribed with P/rOD
Levothyroxine	7	Monitor TFTs [¶] monthly when co-prescribed with P/rOD
Beta blockers	6	Monitor BP [‡] when bisoprolol co-prescribed with SOF/LDV
Rifaximin	4	Monitor for potential increased rifaximin exposure when co-prescribed with SOF/LDV in patients with cirrhosis
Warfarin	4	Monitor INR [±] with all DAA regimens.

†TDF = Tenofovir disoproxil fumarate; ‡BP = Blood pressure; §HR = Heart rate; ¶TFTs: Thyroid function tests; ±INR = International normalised ratio.

Acceptance of pharmacist-led DDI management plans

A total of 477 DDI management recommendations were given to prescribers. The rate of acceptance of pharmacist-led DDI management plans was high overall, at 96.9% (N = 462). Actionable management interventions were accepted in 100% of cases in this study. In cases of potentially severe DDIs, 100% of pharmacist-developed management plans were accepted (Table 2.11).

Table 2.11 Acceptance of pharmacist DDI management recommendations stratified by potential DDI severity.

	N = 477 (%)
Potential Drug-drug interaction Severity Rating	Acceptance of proposed Drug-drug interaction management recommendation
Mild, n (%)	179 (93.2)
Moderate, n (%)	215 (99.1)
Severe, n (%)	68 (100)

Patient outcomes

SVR12 was achieved by 92.7% of the study population. Treatment was self-discontinued by eight patients, none of whom achieved SVR. Five patients were lost to follow up post HCV treatment completion. HCV relapse occurred in nine patients between the SVR 4 and SVR 12-time points. For these cases, the pre-treatment pharmacist assessment process was repeated by a different clinical pharmacist. No new or previously unidentified DDI issues were identified which may have contributed to DAA treatment failure. Retrospective resistance analysis of baseline viral load samples identified that three patients whom experienced HCV relapse had NS5A resistance associated mutations present at baseline, which may have impacted treatment efficacy. No patient within the study group discontinued treatment due to a suspected adverse drug event driven by a DDI between DAAs and co-medications. Statistical analysis found that identification of a potential DDI as part of the pre-treatment pharmacist assessment was not associated with a reduction in SVR attainment (OR 1.38 [CI 95%: 0.36,5.28; p: 0.73]).

Limitations of these studies

Study 2: Analysis of the potential severity of risk associated with medication reconciliation variances.

- The small number of peer reviewers and the fact that all reviewers were from one healthcare profession in some way limits these results.

Study 3: Drug – drug interactions between DAAs and co-medications

- This study did not include the more newly licensed DAAs including grazoprevir, elbasvir, glecaprevir, pibrentasvir, voxilaprevir or velpatasvir. However, the practices of medication reconciliation and DDI review and management described in this study are applicable to all treatments utilised in HCV care. The regimen P/rOD is no longer recommended for first-line use in the US however it is still included in the European guidelines for treatment of genotype 1b infection (60, 61). This study contains a high proportion of patients with HIV; however, it is representative of the patient case mix at the study site. There was no control arm in this study.
- Odds ratio analysis: In some cases, the odds ratio can exaggerate the level of association with a particular risk factor. Relative risk analysis will be considered for use as part of further research work in this area.

2.1.4. Key study findings

What was known prior to this study?

- Studies to date have advocated the beneficial effects of medication reconciliation at the point of hospital admission.
- No published research which has examined the HCV outpatient medication reconciliation process, types of variance identified and their associated significance.
- No published research describing pharmacist-led management strategies for DAA DDIs and patient outcomes.

What is the added value of this study?

- This research provides valuable information on the process of medication reconciliation in an outpatient setting.
- It highlights that the rate of medication variances in the outpatient setting is similar or higher to that reported in the inpatient medication process
- Pharmacist-led DDI review identified that a significant proportion of patients were at risk of clinically significant DDIs
- DDIs between co-medications and DAAs, classified as potentially severe, affected 14% of the study population.
- The acceptance rate of pharmacist-led DDI management plans was high overall, at 96.9%.
- This study has re-enforced the role of the pharmacist as a key component of the HCV MDT.
- Hepatitis C pre-treatment pharmacist DDI review identified that a significant proportion of patients were at risk of clinically significant DDIs between co-medications and direct acting antiviral therapy.

Implications of the new findings?

- It is through the process of pharmacist-led medication reconciliation that an accurate patient medication list can be obtained to ensure the most appropriate HCV DAA treatment is selected and all potential DDIs are effectively managed.
- Pharmacist-led medication reconciliation and DDI assessment are key roles in the stewardship of DAAs to ensure optimum patient outcomes and to reduce the risk of drug-related problems

2.2. Complementary and Alternative Medicines

2.2.1. Introduction

Attaining SVR during the era of treatment with IFN and RBV therapy was challenging, with treatment failure or discontinuation a common occurrence. During this time the use of complementary and alternative medicines (CAM) among HCV seropositive patients was first recognised. Studies completed during the IFN treatment era identified a growing trend of CAM utilisation among this patient cohort. Use was aimed at both complementing ongoing IFN-based HCV treatment and also to provide relief from symptoms felt to be associated with liver fibrosis (237-241).

One of these studies, conducted among US Veterans identified use of multivitamins and herbal supplements to be significantly higher among patients chronically infected with HCV than among a control arm of patients not infected with HCV (237). The most common herbal products identified were milk thistle, ginseng, and echinacea (237). Research investigating CAM use among a French patient cohort identified widespread use of vitamins and dietary supplements (18.1%), herbal medicines (16.8%) and homeopathic products (1.5%) among HCV patients (239). A previous Irish study examining the use of CAM among patients iatrogenically infected with HCV found a high level of use among female patients, those with fibromyalgia and patients with a history of anxiety (241).

Indeed, among the population as a whole use of CAM has been increasing steadily over the last 30 years. A 1999 general population survey in the US found that 28.9% of adults used at least one CAM in the preceding year, with 9.8% using herbal products (242). A survey from Europe involving six countries (Finland, Germany, Italy, Romania, Spain, and the UK) found that among 2,359 consumers, 18.8% admitted using one or more plant food supplements (243). Predictors of CAM use identified in previous research include annual income, years of education and prior hospitalisation for liver disease management (237, 239). A pilot study by Hayward *et al* looking at

co-medications among patients with liver cirrhosis identified significant discrepancies between patient-reported CAM usage and the information documented in their medical records as disclosed to their medical team. When patients within the study group were initially asked to list their medications, only 31.8 % of OTC and CAM products were disclosed by patients. Further questioning about OTC products and CAMs was required to identify these medications. In total, 54% of study patients (N = 27/50) reported taking CAM products with 14.5 % of CAM recorded in the medical record (244).

It must be remembered that the use of multiple medications, herbs or nutritional supplements can have adverse consequences. No herbal products have been studied in well-designed controlled trials of patients with liver impairment or other co-morbidities (242). Issues of concern with regard to CAM products include confirmation of product strength or potency, potential contamination and inaccurate product information. With the advent of highly effective DAA therapies the need for additional treatments to aid HCV therapy response is removed. It is now the case that use of CAM among the HCV treatment cohort may compromise or have negative implications for the outcome of HCV DAA therapies and for patient health overall.

In addition to reviewing prescription and non-prescription medications, it is important for clinical pharmacists to evaluate the use of CAM. The growing risk of DDIs associated with herbal supplements and multivitamins was highlighted in a study by Langness *et al*, with 36% of patients identified as at risk of a DDI between prescribed DAAs and herbal supplements or vitamins (220).

One study showed that silymarin (milk thistle) was commonly used by patients with chronic HCV (16% had used previously and 17% used regularly) treated with IFN and RBV-based therapy to modestly improve HCV treatment response and decrease adverse effects. Concomitant use of silymarin with simeprevir has been shown to increase levels of simeprevir, therefore, clinical

pharmacists should recommend against combining these agents (22). Another CAM to consider is St. John's wort, as it has been shown to decrease serum concentrations of DAAs (233).

For patients being assessed for DAA therapy it is imperative that use of these products is identified and assessed to remove any potential for a negative impact on patient safety or HCV treatment outcome. A high rate of use of multivitamins, mineral supplements and other complementary and alternative medicines (CAM) was identified during the medication reconciliation study. A growing risk of DDIs between CAM products and HCV DAAs has been highlighted in published research however there is no published research on CAM usage rates and patterns among patients with HCV infection in the DAA era. Currently, there is minimal data regarding DDIs with CAM therapies in patients receiving DAA therapy. The University of Liverpool currently provides DDI information for 32 vitamins, minerals and herbal products on its internet DDI checker (233).

2.2.2. Method

Study Design & Setting

A cross-sectional, observational study with a convenience sample conducted at two outpatient clinics at St. James Hospital. This study employed a survey methodology to achieve the study aims.

Sample Size

The total number of patients booked for attendance at HCV outpatient clinics each week was 65. The rate of non-attendance was 20%, thus the pool of patients per week was estimated to be approximately n=52. The patient cohort were very familiar with completing questionnaires and surveys and a positive response rate of 25% was anticipated (i.e. 13 patients per week). Based on capacity to administer the semi-structured interview over a 15-minute time frame, it was anticipated that 5 patients per week would be interviewed by one interviewer. Therefore, over a ten-week interview period, it was anticipated that fifty patients would be interviewed. If patients

expressed a willingness to participate in the study outside of clinic time, this was facilitated, where possible, to increase the patient study sample.

Study Population

Inclusion Criteria

- Patients >18 years of age whom are currently HCV seropositive were invited to participate in the study.

Exclusion Criteria

- Patients with cognitive impairment
- Patients under the influence of illicit substances at the time of the interview

Objectives

- To identify, quantify, describe and categorise use of complementary and alternative medicines (CAM) among a HCV seropositive patient population at a hospital outpatient clinic.
- To measure patient perception about CAM use among a HCV seropositive patient population.

Primary outcome measures

- Prevalence of CAM product use among the patient population
- Identify CAM product types in use among the patient population
- Assess the level of patient knowledge in relation to CAM products
- Establish the rationale for CAM product use by the patient population

Research Ethics Approval

Ethics approval was obtained from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee in May 2017 (Appendix 8). First application: REC 2017-05; Chairman's action (22). Date approved: 31/05/2017. Amendments application: REC 2019-04; List 13 (15). Date approved: 17/04/2019

During the lifetime of this research project, the 2018 Health Research Regulations and EU *General Data Protection Regulations (GDPR)* came into effect. Data collection as part of this research project was initiated in 2017. Patient consent was obtained at the time of data collection. However, with the implementation of the new regulations stated above, patient information leaflets and consent forms were re-formatted to ensure compliance with regulations and the definition of explicit consent. The reformatted patient information leaflet and consent form were submitted to, and approved by, the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee and the St. James's Hospital Data Protection Officer in April 2019. Any patient who had already participated in the research project was reconsented using the updated patient information leaflet and consent form.

Survey design

This study employed a survey design to achieve the study aims. The term CAM, was used to encompass vitamins, minerals, herbal supplements, herbal teas, homeopathic preparations or gym supplements for the purposes of this study.

A study survey instrument was developed to facilitate one-to-one semi-structured interviews with study participants (Appendix 9). A pilot of the survey instrument was undertaken with five patients. This prompted revision of two survey questions. The survey consisted of both closed and open questions to allow a broad range of views and attitudes to be captured. The survey was comprised of three sections:

- a) Background information including patient demographics, including a self-reported quality of life (0-10 score) and education level
- b) Use of CAM
- c) Questions for patients who reported no CAM usage.

Patient quality of life assessment: While this was not one of the primary objectives of this study a question on patient self-reported quality of life using the visual analogue scale (VAS) was added. There are many different types of scoring systems in use in research to assess patient quality of life. For example, the EuroQol- 5 Dimension which asks five questions relating to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (245). One of the domains within the EQ-5D is the VAS where the participant is requested to score their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status)(245). Another possible tool for use in measuring patient quality of life is the Short Form (SF) 36 health survey questionnaire. The SF-36 measures eight scales: physical health and functioning, pain, general health, vitality, social functioning, emotional wellbeing, and mental health (246).

Based on the primary outcome measures of this study a decision was made to ask patients two specific question on quality of life and for this they were asked to use the VAS score to self-report their quality of life and also to describe their health using one of the following descriptors, excellent, very good, good, fair or poor.

Patient interviews were completed at specified times in tandem with the routine HCV clinics at St. James's Hospital. (Tuesday, Wednesday and Thursday mornings). Clinical data pertaining to patient co-morbidities and co-medications were obtained from the patients' electronic and paper medical notes.

Participant recruitment/selection/randomisation

A convenience sampling method was used to recruit patients for this study. Posters were prepared and displayed in the HCV clinic outpatient waiting room from week 1 of the study period to inform patients about participation in the study. Patients were invited to participate in the study while waiting for their routine HCV clinic visit at St. James's Hospital.

Patient consent

The survey was administered to patients who consented to participation in the study in a designated room in the outpatient clinic. Patients were provided with a patient information leaflet and allowed time to consider, before agreeing to take part in the study and then signing the patient consent form. Patients were informed of their right to decline participation in the study. Based on feedback from a previous study, the patient information leaflet and consent form were combined but a copy of the patient information leaflet was available for patients to retain. (Appendix 10)

Data collection & management

Survey data was collected on a paper survey form initially and then exported into Microsoft Excel® in a fully and irrevocably anonymised format using a defined data codebook. Patient data collected from electronic and paper-based medical records was entered directly into the Microsoft Excel® database.

The study dataset underwent a systematic quality control procedure according to a process described by van den Broeck *et al* to ensure the rigour to the results, as data entry, particularly patient interviews can be subject to input errors (247). Therefore, a double data entry protocol was undertaken for a random 10% of the surveys to determine the extent of errors. The cleaned database was then analysed. Data analysis was undertaken in St. James's Hospital.

Primary access to the anonymised database was restricted to the primary researcher and an assigned research student. Project data was held on a secure server in St. James's Hospital. St. James's Hospital have strict data protection measures in place. Data confidentiality was ensured at all times. After completion of data analysis, the electronic database will be retained for 5 years on the secure server. After this time has elapsed, the data will be destroyed/deleted.

Statistical analysis

Descriptive statistics were used to present the study data. Data collected as part of the study was both categorical and continuous. Statistical analyses of the study findings were performed using IBM SPSS (version 24.0) with significance levels set at $P \leq 0.05$. T-test analysis was completed to investigate if patient reported quality of life was influenced by use of CAM products. The level of association between specific patient characteristics was assessed using calculation of the Chi² statistic.

Survey data analysis

Narrative comments were analysed using a grounded theory approach to identify emerging themes. This process was completed by the primary investigator. Grounded theory is a method of data analysis which aims to construct a theory for the occurrence of a phenomenon (in this case use of CAM products among patients with HCV infection) (248). Grounded theory involved constant comparison of the data collected with the aim of identifying patterns of behavior. Data was coded and categorised to refine key concepts identified in the research data gathered (248).

2.2.3. Results

Participant Demographics

A total of 50 patients consented (from a total of 77 patients approached) to be included in this study of whom 70% (N = 35) were male (Table 2.12). Double data entry checking for a random 10% of the surveys, identified two minor data entry errors for one survey entry. The average age of the study population was 45 ± 12 years while the average number of co-morbidities among patients in the study cohort was two. In addition to chronic HCV infection, common co-morbidities included depression and anxiety, HIV co-infection and diabetes (Table 2.12). Among the study population, 88% were taking at least one medication (N = 44).

Table 2.12 Patient Demographics of CAM study population

Patient Demographics	N = 50 (%)
Age at time of pharmacist review (mean ± SD) (Range), years	45 years ± 12 (25-75)
Male, n (%)	35 (70)
Presence of cirrhosis, n (%) *	13 (26)
Route of HCV acquisition, n (%)	
PWID	33 (66)
Sexual transmission	9 (18)
Infected blood products	4 (8)
Vertical transmission	0 (0)
Unknown risk	3 (6)
Origin from country of high prevalence	1 (2)
<i>Country of origin, n (%)</i>	
Ireland	31 (62)
Other EU countries	13 (26)
Non-EU countries	6 (12)
<i>Education level attained, n (%)</i>	
Primary level education	1 (2)
Secondary level education	27 (54)
Third level education	17 (34)
Unknown	5 (10)
<i>Employment Status, n (%)</i>	
Employed	27 (54)

Retired	6 (12)
Student	1 (2)
Unemployed	16 (32)
No. of co-morbidities (Mean \pm SD (Range))	2.2 \pm 1.4 (0-5)
Types of co-morbidities, n (%)	
Gastro-intestinal conditions	5 (10)
Depression/ Anxiety	11 (22)
HIV co-infection	21 (42)
Respiratory conditions	3 (6)
Cardiovascular disease	5 (10)
Diabetes mellitus	6 (12)
Osteoporosis	2 (4)
Chronic pain	2 (4)
Hypothyroid	1 (2)
Dermatological conditions	1 (2)
No. of concurrent medications (Mean \pm SD (Range))	3.9 \pm 2.8 (0-12)

*Defined as cirrhotic if fibroscan >12.5kPa in HCV mono-infected patients and if fibroscan >10kPa in patients whom are HIV co-infected.

SD: Standard deviation; HCV: Hepatitis C; PWID: People who inject drugs; EU: European Union; HIV: Human immunodeficiency virus.

CAM use

Among the study population (N = 50), 44% reported use of CAM (N = 22). A total of 54 reports of CAM product usage were identified among the survey participants (Range 0-8 CAM products per patient). The average number of CAM in use per patient was one (1 ± 1.8). The most commonly used CAM products were gym supplements, herbal teas and milk thistle (Table 2.13).

Table 2.13 CAM product use reported

CAM Product	No of patients reporting use
Gym supplement: Whey protein/creatine	8
Herbal Teas	8
Milk Thistle	3
Multivitamin products	3
Homeopathic tincture	2
Liver herbs mixture	2
Spirulina	2
Vitamin C	2
Vitamin D	2
Acidophilus	1
Branch Chain Amino Acids (BCCA)	1
Chia Oil	1
Cod Liver Oil	1
Cranberry supplement	1
Echinacea	1
Evening primrose oil	1
Fish oils	1
Magnesium supplement	1
Nux Vom	1
St. John's Wort	1
Weight loss tea	1

Patient self-reported quality of life

When asked to rate their general health status as excellent, very good, good, fair or poor, 70% of the study participants rated their health as good, very good or excellent (Table 2.14). Among the study population, 10% (N = 5) reported feeling that their activity was limited by illness or disability with three patients reporting that they had been hospitalised previously for management of their liver health.

In terms of self-reported quality of life scores (0-10, with 10 being excellent) among the survey participants, a mean score of 6.7 was recorded, with no statistically significant difference identified between scores reported by CAM versus non-CAM users ($T: 0.137; p > 0.05$).

Table 2.14 Patient self-reported health status

Patient reported general health status	No of patients N = 50	CAM users N = 22	Non-CAM users N = 28
Excellent	4	1	3
Very good	10	7	3
Good	21	10	11
Fair	11	2	9
Poor	4	2	2

Rationale for CAM use

Among the cohort of patients who reported CAM use, a variety of reasons for use were observed. The two most prevalent reasons for use were to improve general health and to improve gym workout results (Table 2.15).

Table 2.15 Rationale for CAM use

Reason for CAM use	Number of patients (N = 22)
To improve general health	6
To improve gym workout results	5
To boost energy	3
Recommendation of family or a friend	2
To promote gut health	2
To promote liver health	2
Recommendation of a healthcare professional	2
To build up the immune system	1
To aid sleep	1
To improve joint health	1
Unknown	1

A significant proportion of patients reported that they had received information about CAM products from family and friends and various media sources. Two patients reported receiving

information directly from a CAM practitioner and three patients received information from a healthcare professional (Table 2.16).

Table 2.16 Sources of information about CAM

Sources of information about CAM	No of patients (N = 22)
Friends and family	15
Internet	4
Healthcare professionals	3
Health food shops	3
TV/Radio/Newspaper/Magazines	2
CAM practitioners	2
Gym	2

Source of CAM products

Sources of CAM products reported included, health food shops (68.2%), community pharmacies (18%), supermarkets (18%), on-line shopping (13.6%), CAM practitioners (including homeopaths) (9%) and the gym (4.5%). CAM practitioners including acupuncturists, homeopaths and herbalists were utilised by nine patients in the study group, who reported an average of two CAM practitioner visits per year with an average cost of €250 per year. Among patients who reported CAM product use there was a wide range in the duration of use (1 month – 15 years). Information on CAM expenditure was more difficult to obtain from patients as many were uncertain of the amount they had spent. Again, a wide range of answers were received (Range €10- €1,400 per year).

A majority of participants using CAM products reported that they did so in combination with OTC and prescription medicines (77.3%, N = 17). Three patients reported using CAM products instead of OTC and prescription medicines with one patient reporting they were unsure. When purchasing CAM products or attending CAM practitioners' the majority of respondents reported disclosing their co-medications sometimes (58.3%), 16.6% stated they always disclosed their co-medications and 25% stated they never disclosed their co-medications when purchasing CAM products or attending CAM practitioners'. When asked if they disclosed use of CAM medicines to HCPs during

consultations, 27.3% (N = 6) reported that they would routinely disclose CAM use. The remainder reported that they never (18%, N = 4) or only sometimes (41%, N = 9) disclose CAM use to healthcare staff involved in their care. Satisfaction rates among those whom utilised CAM products varied greatly (Mean 4.7; Range (1-10)). However, the majority of respondents (68%) reported that they felt CAM use had made their health better.

Patient comments on CAM use;

“My body felt better when I started taking gym supplements.”

“I feel like I have so much more energy when I am taking my supplements”.

“CAM use is the reason I have been so healthy all of my life”.

Patient characteristics and their potential association with CAM use

An association between CAM use and younger age was identified within the study population (mean age of patients reporting CAM use was 41 years versus 48 years in the non-CAM use group), however this was not found to be statistically significant (p 0.55) (Table 2.17). No association was identified between liver disease staging (fibroscan score) and use of CAM products (T : 0.396; p : 0.694). The only patient factor found to be linked with CAM usage was attainment of a third level education (Chi squared statistic: 7.059; p <0.05) (Table 2.17). This link was found to be statistically significant.

Table 2.17 Patient characteristics and association with CAM use

Patient characteristic	Association with CAM use Chi ² statistic (<i>p</i> -value)
HIV co-infection	0.19 (0.661)
Diabetes	2.07 (0.15)
Psychiatric co-morbidity	0.18 (0.669)
Gastrointestinal co-morbidity	0.04 (0.849)
Cardiovascular disease	1.3 (0.254)
Third level education achieved	7.059 (0.05)

Potential for drug-drug interaction between CAM products identified and HCV therapy

Each of the CAM products reported were assessed as part of the patient medication reconciliation process prior to patient progression to HCV treatment. Multiple products were identified as having the potential to interact with HCV DAAs and therefore patients were requested to discontinue these CAM products while receiving HCV therapy. Patients were also requested to discontinue certain CAM products due to uncertainty about the exact product constituents and a lack of DDI information for certain herbal products. These products included St. John’s wort, green tea preparations, some gym supplements, weight loss tea, spirulina and some homeopathic products.

Non-CAM users

The majority of the study population did not report CAM product usage (56%, N= 28). Among those not using CAM products, ten patients reported that they had considered using these products previously with seven patients reporting that CAM product use had been recommended to them. A lack of knowledge around CAM product use was reported by the majority (60.7%) of this patient group. Reasons for not using CAM products included a lack of evidence to support their use, a fear

that these products could affect their current co-medications or medical conditions or no current unmet medical requiring their use.

Limitations of this study:

- The rate of CAM use reported was higher among the survey cohort than the rate identified in the medication reconciliation and DDI study. This may in part be due to the fact that a convenience patient sampling method was used and therefore patients who agreed to participate in this study may have done so because they were aware of, and were already using, CAM products. However, this does not take away from the fact that regardless of the proportion of patients using CAM it is important that patients undergo the process of medication reconciliation as part of their HCV treatment workup so that usage of these products is identified, assessed for the potential for DDI with HCV DAAs and other co-medicines and also assessed in terms of safety of use based on the patients liver fibrosis status.
- Another limitation of a convenience sampling method is the limitation of generalisability of results from the convenience sample. Convenience sampling meant that only patients treated for HCV infection at St. James's Hospital were recruited. There are six other HCV treatment sites in Ireland where patients may have very different CAM usage practices.
- This was a single site study.
- It is unclear whether other studies considered gym supplements as CAM products. There is a wide variety of CAM definitions in use which does make the comparison of rates of CAM use between different studies difficult. However, there is a growing trend in use of gym supplements and they need to be considered in terms of their risk of DDI and also their potential to be hepatotoxic or lead to other adverse health effects.
- As is the case in survey-based research, the self-reported nature of the data is a limitation because there is no independent verification of its accuracy.

- Social desirability may have led to bias in some responses. For example, when patients were asked if they disclosed information about CAM use to HCPs, some patients may have said yes as they wanted to appear to have done the right thing.
- Some of the survey questions utilised a closed question design which may have limited some the range of responses received for these questions.
- Quality of life measure: Patient quality of life was not the primary research outcome measure of this survey. Other measures for this parameter could have been used including, EQ5D and SF-36 (245, 246) which would have provided more domain specific information.

2.2.4. Key Findings:

What was known prior to this study?

- Use of CAM was recognised in the interferon era.
- There has been no published research on CAM use among HCV patients in the DAA era

What is the added value of this study?

- This represents the first research identifying the rate of CAM use among HCV patients in the DAA era.
- A high proportion of patients reported CAM product use. Therefore, HCPs caring for people with HCV should ask patients about their use of these products during patient consultations.
- The majority of patients using CAM products do so in conjunction with conventional medicine.
- The majority of patients using CAM products do so in conjunction with conventional medicine. However, they do not always disclose use of CAM to HCPs. It is important that the potential for DDI between CAM products is assessed with patient co-medications including when DAA therapy is being prescribed.
- There is the potential for DDI between CAM products and HCV DAA therapy.

Implications of the new findings?

- Healthcare professionals caring for people with HCV infection should specifically ask patients about their use of these products during consultations.
- It is important that the potential for DDI between CAM products is assessed with patient co-medications including when DAA therapy is being prescribed

2.3. Treating Hepatitis C in patients with epilepsy. A drug-drug interaction dilemma

2.3.1. Introduction

Epilepsy is a heterogeneous and serious brain disorder with multifactorial origins and manifestations. Epilepsy is the second most common neurological disorder after stroke (249, 250). It is estimated that worldwide approximately 50 million people or 3% of the population have epilepsy. This represents the same burden of disease as lung cancer in men or breast cancer in women (249, 250). It comprises many seizure types, which can impose significant restrictions on everyday life such as driving, work activities and social interaction, all of which have a significant impact on quality of life (250, 251). In Ireland it is estimated that 37,000 people have epilepsy (249). The prevalence of epilepsy among the HCV treatment cohort in Ireland is 2.7% (236). The global burden from epilepsy as measured by disability adjusted life years increased by 30% between 1990 and 2010. In addition to psychosocial disabilities and seizure related injuries, epilepsy is associated with other co-morbidities including depression and increased mortality (249). In 2010, the disease burden from epilepsy was higher than that for Alzheimer's disease and other dementias, multiple sclerosis, and Parkinson's disease combined (250).

Overall mortality in people with epilepsy is three times (24%) the rate expected in the general population and more than half the deaths were related to epilepsy itself, including sudden unexpected death which accounted for a third of all deaths (250). Jepsen *et al* have previously shown that patients with liver cirrhosis who have been given a diagnosis of epilepsy have a higher mortality than other patients with cirrhosis (252).

The management of epilepsy requires a long-term, multidisciplinary, co-ordinated care approach that empowers patients towards pro-active management of their condition (249). AEDs are the mainstay of epilepsy treatment. AED monotherapy is effective in the treatment of epilepsy in 60–70 % of patient cases (250, 253, 254). However, for the remaining 30% of patients, treatment can

be more complex, requiring AED polypharmacy to achieve seizure control (249, 251). About 20-30% continue to have drug resistant epilepsy with seizures, adverse effects, increased mortality, and substantial psychiatric and somatic comorbidities (251).

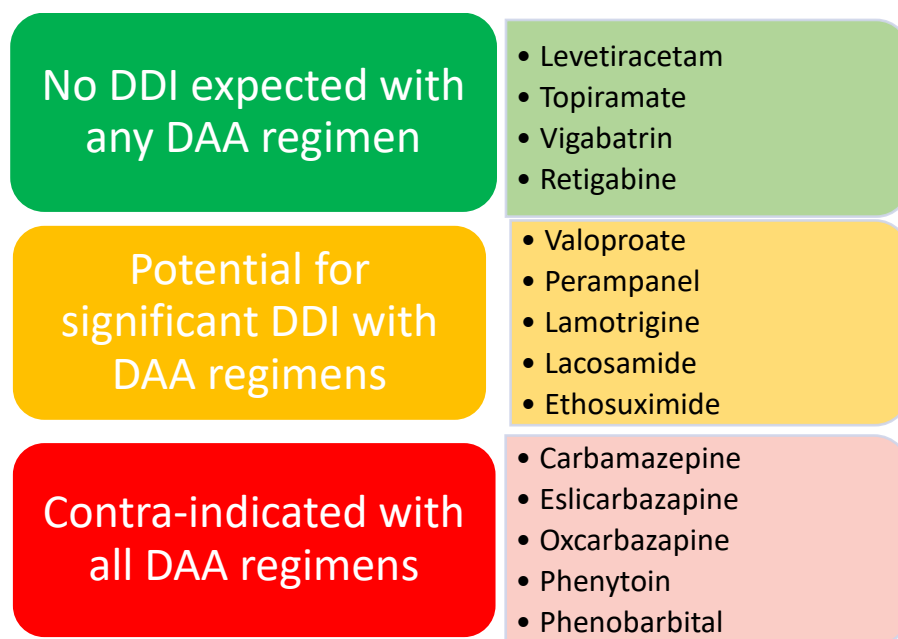
AEDs are categorised into first and second-generation AEDs (e.g. phenytoin, phenobarbital and carbamazepine) and newer third generation AEDs (e.g. lacosamide, perampanel and eslicarbazepine) according to when they were first licensed for use. Choice of AED is guided by seizure type and patient characteristics (Table 2.18).

Table 2.18 Recommended AED options for treatment of specific seizure type.

Seizure Type	Potential 1st Line Treatment Options
Tonic/Clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate
Tonic/Atonic	Sodium valproate
Absence	Ethosuximide Lamotrigine
Myoclonic	Levetiracetam Sodium valproate Topiramate
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine

A significant factor in terms of AED choice is the potential for DDIs to occur. AEDs as a therapeutic medication class are associated with more DDIs than any other class of medications (253, 254). The CYP450 family of enzymes and the UGTs play an important role in AED metabolism (254). AEDs which induce these metabolic pathways and transporters pose a significant potential for interaction with other medications. The older AEDs in particular (e.g. carbamazepine) are more prone to DDIs although some of the newer AEDs can also be problematic (e.g. eslicarbazepine) (249). Overall, the

third generation AEDs have less interaction potential, primarily because many are renally excreted or not hepatically metabolised (e.g. lacosamide and levetiracetam) and most do not induce or inhibit hepatic metabolism (253) (Figure 2.15). However, the risk is not completely eliminated as in the case of eslicarbazepine which is also an inducer of CYP 450 isoenzymes (233).



DDI: Drug-drug interaction; DAA: Direct acting antiviral

Figure 2.15 Anti-epileptic medication drug-drug interaction potential with Hepatitis C direct acting anti-virals.

Several clinical scenarios require patients to be switched to a non-enzyme inducing AEDs. Examples include patients who need pharmacotherapy for cancer or those with other life-threatening diseases treated with drugs that are inducible by concurrent AED drug treatment (251). Switching patients to non-enzyme inducing drugs to avoid these interactions should be done with caution, particularly if seizures are not already fully controlled. For seizure-free patients, the risks and benefits of switching need to be carefully weighed given the paucity of data on comparative likelihood of seizure control. In all such situations, the benefits and risks of both courses of action should be discussed with patients and their families (251).

This high risk of DDI occurrence has the potential to impact treatment of patients with HCV infection who also have co-morbid epilepsy (Figure 2.15). For example, focal seizures represent the most common type, accounting for 60% of all seizures (249). However, two of the first line treatment options for this seizure type are contra-indicated with all currently available DAAs regimens (Figure 2.15) (233). In addition, both the Scottish Intercollegiate Guideline Network and the International League Against Epilepsy rate phenytoin and carbamazepine as the AEDs with the highest quality of efficacy and effectiveness data across all seizure types (5, 6). However both of these AEDs are contra-indicated with all HCV DAA regimens (233).

Patients with HCV infection who are co-prescribed AEDs for management of epilepsy represent a major therapeutic challenge in terms of AED DAA drug-drug interactions. These DDIs may have a negative impact on both seizure control and HCV treatment outcome. (Table 2.19) The potent induction of CYP 450 isoenzymes and transport proteins by several AEDs including carbamazepine, eslicarbazepine, phenytoin, phenobarbital and oxcarbazepine has the potential to significantly reduce DAA exposure which in turn may result in HCV treatment failure with emergent resistance (233). The potential for these potent enzyme inducing AEDs to reduce the therapeutic levels and efficacy of HCV treatment is present with all licensed DAA regimens and all regimens currently contraindicate co-administration. DDIs between DAAs and AEDs can also lead to a reduction in potential efficacy of an AED regimen (e.g. reduced lamotrigine exposure with co-administration of P/rOD) or an increase in AED exposure which may increase the risk of AED related side effects and patient morbidity (e.g. increased lacosamide or perampanel exposure when co-administered with P/rOD) (233). (Figure 2.15)

Table 2.19 Currently licensed antiepileptic drugs and their metabolic pathways.

AED	Inhibition of pharmacokinetic pathways	Induction of pharmacokinetic pathways	Substrate of
Eslicarbazepine	CYP2C19 (Moderate)	CYP3A4 (Weak), UGT1A1 (Moderate)	CYP3A4
Carbamazepine	CYP2C19	CYP3A4 (Potent), P-gp (Potent), CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A5, CYP3A7, CYP2C19	CYP3A4, CYP3A5, CYP3A7
Oxcarbazepine	CYP2C19	CYP3A4 (Potent), CYP3A5 (Weak), CYP3A7, P-gp (Potent), UGT (Weak)	CYP450 isoenzymes
Phenobarbital	Nil	CYP3A4 (Potent), CYP2B6, CYP2C9, CYP2C8, CYP3A5, CYP3A7, P-gp (Potent)	CYP2C19
Phenytoin	Nil	CYP3A4 (Potent), CYP2B6, CYP2C8, CYP3A5, CYP3A7, P-gp (Potent)	CYP2C9, CYP2C19
Lacosamide	CYP2C9		CYP3A4
Lamotrigine	Nil	Nil	UGTs, UGT1A4
Perampanel	Nil	CYP3A4	CYP3A4
Topiramate	N/A	N/A	Not extensively metabolised.
Levetiracetam	N/A	N/A	Not extensively metabolised.
Sodium valproate	Nil	Nil	Glucuronidation (Major) CYP2C9 (Minor)

AED: Anti-epileptic medication; CYP: Cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: P-glycoprotein

If a change in AED treatment is required to overcome a potential DDI, patients may be switched gradually to monotherapy with another drug or combination therapy may be considered (250). With more than twenty AEDs currently available, there are options available to individualise patient therapy based on their specific co-morbidities and co-medications however this process of change

must be undertaken slowly and cautiously under the supervision of a neurologist to avoid any impact on seizure control (250).

Thorough assessment of potential DDIs with AEDs is required prior to initiation of treatment for HCV infection, to determine their impact on treatment outcomes and to initiate appropriate management interventions. To date, there is a paucity of literature on the management of HCV DAA therapy in patients with epilepsy in a real-world setting (236, 255-257). Patients with epilepsy were chosen as a sub-study population due to the high rate of severe DDIs identified between AEDs and DAAs in the previously described DDI study. In addition, medications used in the treatment of epilepsy among the patient cohort of the medication reconciliation study accounted for four high risk variance episodes.

2.3.2. Method

Study Design & Setting

A retrospective cohort study of patients with chronic HCV infection and co-morbid epilepsy treated with DAAs at HCV hospital treatment sites in Ireland (N = 22).

Study Population

All patients with a co-morbid diagnosis of epilepsy, taking at least one anti-epileptic medication (AED) at baseline, who were assessed for DAA-based HCV treatment at one of four Irish hospital outpatient clinics between December 2014 and June 2017 were included in this retrospective analysis of pre-treatment pharmacist assessment utility and outcomes. Patients prescribed AEDs for indications other than epilepsy management were excluded from this study.

Objectives

- To assess the prevalence, severity and management of potential DDIs associated with AEDs identified as part of HCV pre-treatment pharmacist assessment
- To measure the impact of AED DDIs on time to HCV treatment initiation.

Research Ethics Approval

The St. James's and Tallaght Hospitals Joint Research and Ethics Committee evaluated and approved the study protocol. (REC Reference Waiver of Ethics Approval 40/17. Date approved: 01/12/2017) (Appendix 11). During the lifetime of this research project, the 2018 Health Research Regulations came into effect. Data collected as part of this research project was collected in Dec 2017 and January 2018 and patient information collected was fully and irrevocably anonymised in February 2018. This project is in compliance with Health Research Regulations and GDPR.

Data collection

The pharmacist assessment captured patient information pertaining to baseline characteristics including laboratory markers, co-morbidities, liver disease status and proposed HCV treatment plan through chart review. The process of pharmacist-led medication reconciliation was completed with all patients included in this study prior to DDI assessment. The medication reconciliation process identified all prescription medicines, OTC products, herbal supplements, multivitamins and other products in use by each patient.

DDI analysis and classification

The DDI assessment employed a standardised reference list including the specialised University of Liverpool website (233). (Appendix 6) A DDI review was completed for each study patient between their list of co-medications, including AEDs, as confirmed by the medication reconciliation process, and the proposed HCV treatment regimen documented in the patient's medical notes. Available licensed DAAs during the study time period were SOF, LDV, DCV, P/rOD and VEL. (Table 2.20). The DAAs were prescribed in four specific drug regimen combinations in accordance with international guidelines.

Table 2.20 Initial choice of Hepatitis C treatment

DAA regimen
Sofosbuvir/ledipasvir (SOF/LDV) † ‡
Sofosbuvir/daclatasvir (SOF/DCV) ‡
Paritaprevir/ritonavir/ombitasvir/dasabuvir (P/rOD) ‡
Sofosbuvir/ribavirin (SOF/RBV) ‡

† For the first five months of the study period DAA access was limited to SOF/LDV. For the remainder of the study period, national prescribing guidelines were in place but access to non-first line regimens was available on physician request to the National Hepatitis C Treatment Programme. ‡ These commonly used and accepted abbreviations for DAA regimens will be utilised throughout this manuscript.

The outcome of the DDI assessment included classification into three descriptive categories, and where a potential interaction was identified or in the absence of data, a significance rating of severe, caution or mild was applied.

DDI management

Where a potential interaction was identified, a number of DDI management recommendations were incorporated into the DDI review to guide patient care prior to commencement of, and during treatment. These included: a) discontinuation of an interacting medication during HCV therapy, b) dose adjustment of an interacting co-medication, c) a change in the interacting medication to an alternative in class or in clinical effect, d) initiation of a monitoring plan, e) a dose time separation strategy and f) consideration of an alternative HCV treatment regimen. DDI management strategies were developed by the clinical pharmacist and communicated both verbally and in writing to the medical teams at the time of review.

Data management

Data collected as part of this study was entered onto a password encrypted Microsoft Excel® database. Data entry onto the database occurred on site at St. James's Hospital using a computer accessible only to staff within the pharmacy department via individual log on details. The database password was only available to two people, the primary investigator and an appointed other. Patient data was fully and irrevocably anonymised. The excel database once complete were transferred to SPSS in a coded format for statistical analysis.

Statistical analysis

Descriptive statistics were used to describe the study cohort. Comparative analysis was performed in order to investigate the impact of prescribed AED therapy on timeline to HCV treatment initiation. Patients were followed up for the duration of the study period. The time from initial pharmacist assessment to treatment initiation was measured for patients in the study group and compared with that of a control group of HCV patients who were also assessed and initiated on HCV therapy but were not prescribed AEDs.

Control group: The control group of patients were anonymised patient cases from the St. James's Hospital HCV treatment cohort (i.e. Patients treated for HCV infection with DAAs at St. James's Hospital who did not have a diagnosis of epilepsy and were not prescribed antiepileptics). These patients were taken from the database of patients treated, held within the Hepatitis C pharmacy service. The control patient group were matched to the AED patient group for age, gender, HCV genotype, liver fibrosis staging and number of co-morbidities.

Analysis including the preparation and interpretation of Kaplan Meier curves along with the calculation of log-rank score and cox proportional hazards were utilised to identify if the presence of AED co-prescription was impacting time to DAA treatment initiation. All statistical analyses were

performed using SPSS for Windows, version 24.0 (IBM SPSS, Chicago, Illinois) [®], with significance levels set at $P \leq 0.05$. Kaplan Meier was chosen as an analysis tool as it estimates the time for an individual or a group of individuals to experience an event of interest, in the case, the time until initiation of HCV treatment.

2.3.3. Results

Patient demographics

A total of 22 patients were included in this review of HCV treatment patients with epilepsy of whom the majority were male (72%). The majority of patients were prescribed AED monotherapy (68.2%). Cirrhosis was identified in 63% of the study cohort with an average of 3 co-morbidities. (Table 2.21). Common co-morbidities among the AED cohort included a history of addiction, depression and thyroid dysfunction. The majority of patients had genotype 1 infection (68.1%), with SOF/LDV the most frequent DAA regimen prescribed.

Table 2.21 Patient Demographics of the epilepsy study cohort

Patient Demographics	AED Group N = 22	Control Group N = 22
Age at time of pharmacist review (years +/-SD ^a) (Range)	50 years +/- 8.75 (25-67)	47 years +/- 8.45 (27-61)
Male	16 (72%)	16 (72%)
Presence of cirrhosis	14 (63%)	14 (63%)
No. of co-morbidities (Mean (Range))	2.68 (0-7) *	3.63 (1-7)
No. of concurrent medication (Mean (Range))	8.5 (2-24)	5 (0-18)
HCV Genotype	G1 [†] : 15 (68.1%) G3: 7 (31.9%)	G1 [†] : 14 (63.6%) G3: 7 (31.8%) Mixed: 1 (4.6%)
DAA Regimen Prescribed	P/rOD: 4 (18.2%) SOF/LDV: 11 (50%) SOF/DCV: 6 (27.3%) SOF/VEL: 1 (4.5%)	P/rOD: 4 (18.2%) SOF/LDV: 11 (50%) SOF/DCV: 6 (27.3%) SOF/VEL: 1 (4.5%)

A: Standard deviation; *Excluding epilepsy; † No differentiation was made between G1a and G1b in this study as DAA treatment choice was not influenced by the genotype 1 subtype.

Medication reconciliation

Following the completion of medication reconciliation, a total of 186 concomitant medicines were identified, including 32 AEDs, requiring screening for potential DDIs. The most commonly prescribed AEDs included levetiracetam, sodium valproate and carbamazepine (Figure 2.16). AED polytherapy was identified in 31.8% of patients including one patient prescribed a regimen of five AEDs. Other commonly prescribed co-medications among the study group included antidepressants, methadone, antiretrovirals and PPIs.

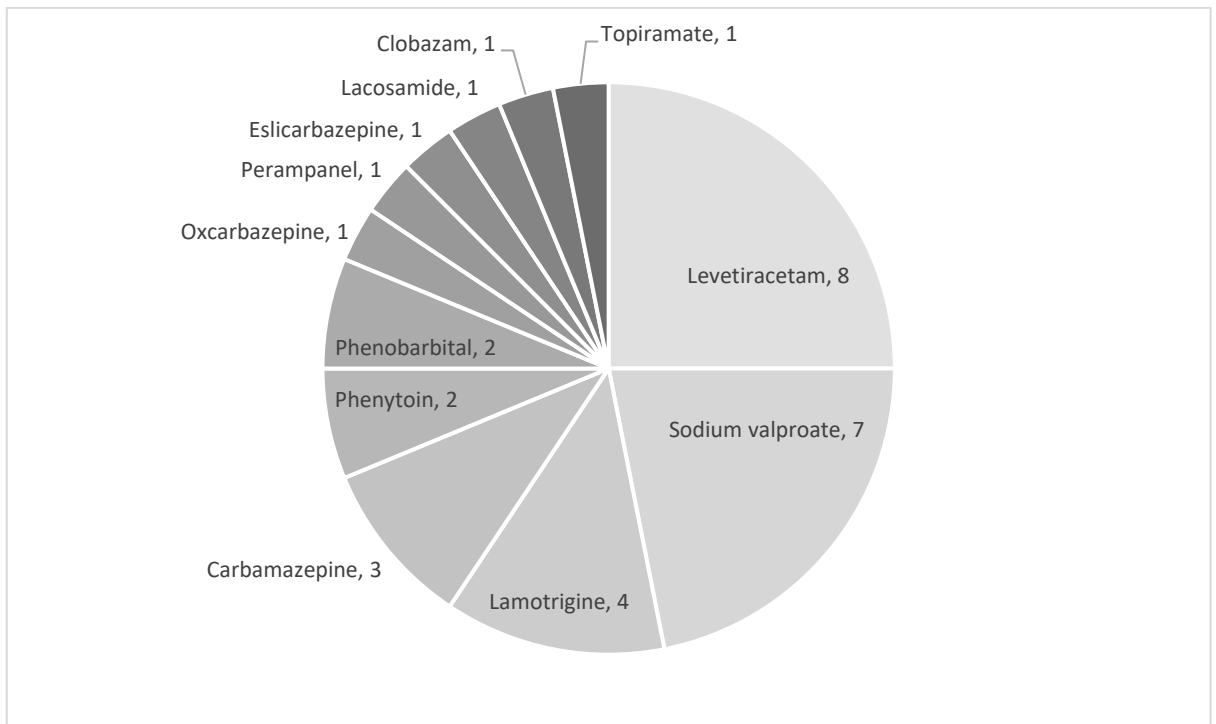


Figure 2.16 Number of anti-epileptic medication prescriptions identified during pre-treatment pharmacist assessments

DDI assessment

The DDI assessment process identified that more than one third of all AED prescriptions (37.5%) were subject to a potential DDI with the proposed DAA regimen, affecting 45.5% of patients. A rating of severe was applied to 75% of identified AED DDIs, with all deemed as having the potential

to reduce DAA bioavailability. In two patient cases, DDIs were identified which had the potential to cause a reduction in AED medication exposure.

Management of AED DDIs

Seven patients required a change in their AED medications to prevent adverse treatment outcomes due to the enzyme inducing effects of AEDs. (e.g. carbamazepine and phenytoin). One patient prescribed sodium valproate and initiated on HCV therapy with P/rOD required therapeutic drug monitoring (TDM) for AED therapy. The proposed DAA regimen P/rOD had the potential to reduce valproate exposure. TDM permitted assessment of any change in drug levels with dose adjustment possible as required (Appendix 24).

Temporary cessation of an interacting AED was necessary for one patient, in conjunction with neurology team input. One patient was treated with an alternative DAA regimen (SOF/LDV) which did not interact with this patient's AED regimen (lamotrigine). TDM was not an available option in this case. All management recommendations arising from the pharmacist DDI assessment process were accepted by the medical teams. All changes in AED regimens were completed in collaboration with neurology services. In all patients where AED regimens were altered to facilitate HCV therapy, new AED regimens were continued post treatment cessation. No patient reverted back to their pre-treatment regimen.

Stratification of the patient cohort based on DDI occurrence and DDI significance

Overall, DDI management in patients with epilepsy was associated with a delay in time to HCV treatment initiation in 54% of patients (mean = 96 days), compared to the control group (mean = 50 days). In order to investigate the impact of AEDs prescribed on time to initiation of HCV treatment, a Cox proportional hazards model was fitted. Analysis between the total AED cohort and the control group did not find a statistically significant difference in timeline to HCV treatment

initiation between the two cohorts (Log rank test $p= 0.104$, HR 1.714 (95% CI 0.885, 3.318). The patients were then stratified into three groups based on potential for, and severity of, AED DAA interactions identified. Statistical analysis was then repeated for each stratified subgroup.

Analysis of the study cohort who were prescribed AEDs which were subject to mild to moderate potential DDIs with DAA therapy found that this group did not have a statistically significantly longer timeline to HCV treatment initiation when compared with matched controls (Log rank test $p = 0.115$, HR 4.959 (95% CI 0.491, 50.03). For patients prescribed AEDs which were not subject to any DDIs with the prescribed DAA regimen there was no link identified to a delay in HCV treatment initiation due to presence of the epilepsy condition itself. (Log rank test $p = 0.586$; HR 0.789 (CI 0.332, 1.872)).

Overall, DDI management in patients with epilepsy was associated with a delay in time to HCV treatment initiation in 54% of patients with epilepsy (mean = 96 days), compared to the control group (mean = 50 days). Comparative analysis between the AED cohort and the control group did not find a statistically significant difference in timeline to HCV treatment initiation between the two cohorts (Log rank test $p= 0.104$). (Figure 2.17)

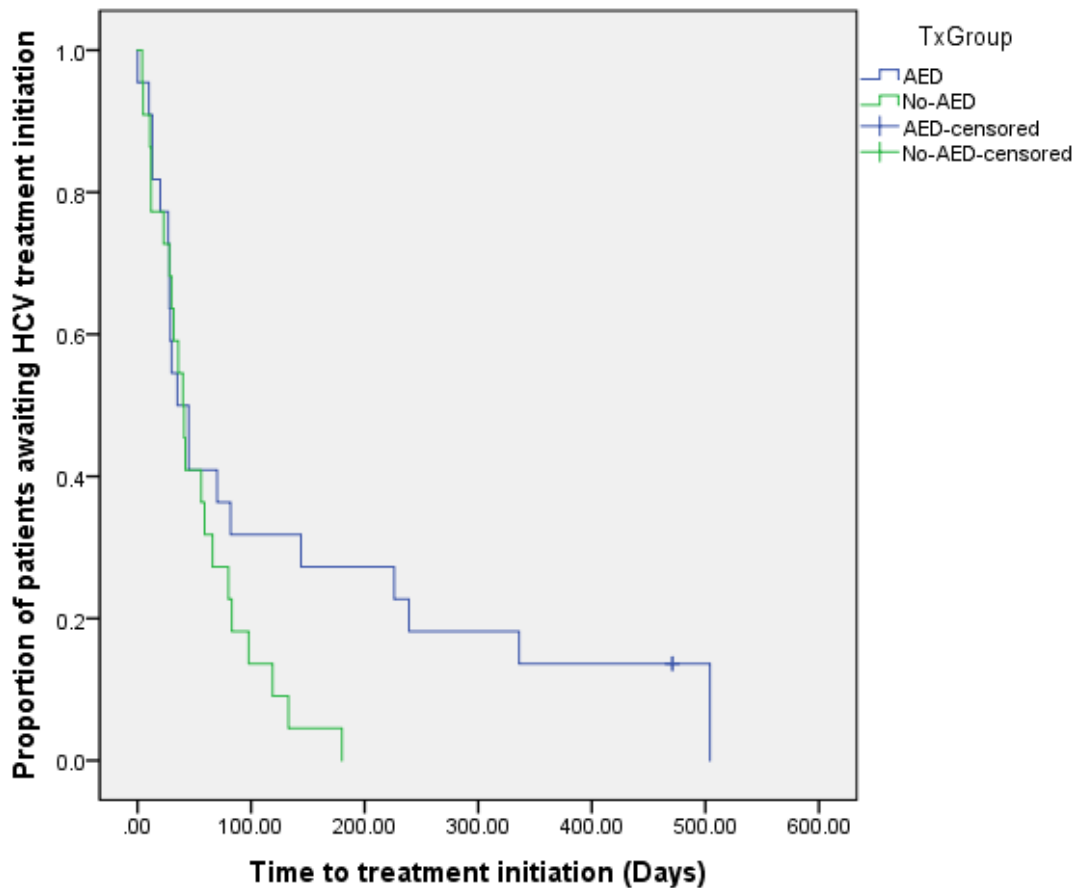


Figure 2.17 Time to Hepatitis C treatment initiation between all study patients receiving AED therapy for epilepsy and a matched control group of patients not prescribed AEDs.

Individual patient cases

Two patients within the AED study group have been unable to initiate HCV therapy to date (Appendix 24). Patient 1 is prescribed a complex polytherapy AED regimen which contains eslicarbazepine. MDT management of this patient involving neurology and hepatology specialists has been unable to remove or replace eslicarbazepine within this patient's AED regimen due to ongoing seizure activity. Eslicarbazepine is currently contra-indicated with all DAAs due to its enzyme inducing effects. Patient 2 requires a prolonged timetable of AED dose de-escalation following long term therapy with high dose phenobarbital and phenytoin which is not yet complete. Among the twenty epilepsy patients whom have initiated HCV DAA therapy to date, all have

completed treatment and the SVR rate is 100%. No patient discontinued treatment and no seizure episodes were reported during treatment in the AED group.

Analysis of the AED cohort who were prescribed AEDs which were subject to severe potential DDIs with DAA therapy found that this group did have a statistically significantly longer timeline to HCV treatment initiation when compared with matched controls (Log rank test $p = 0.006$, HR 5.652 (95% CI 1.428, 22.379)). (Figure 2.18)

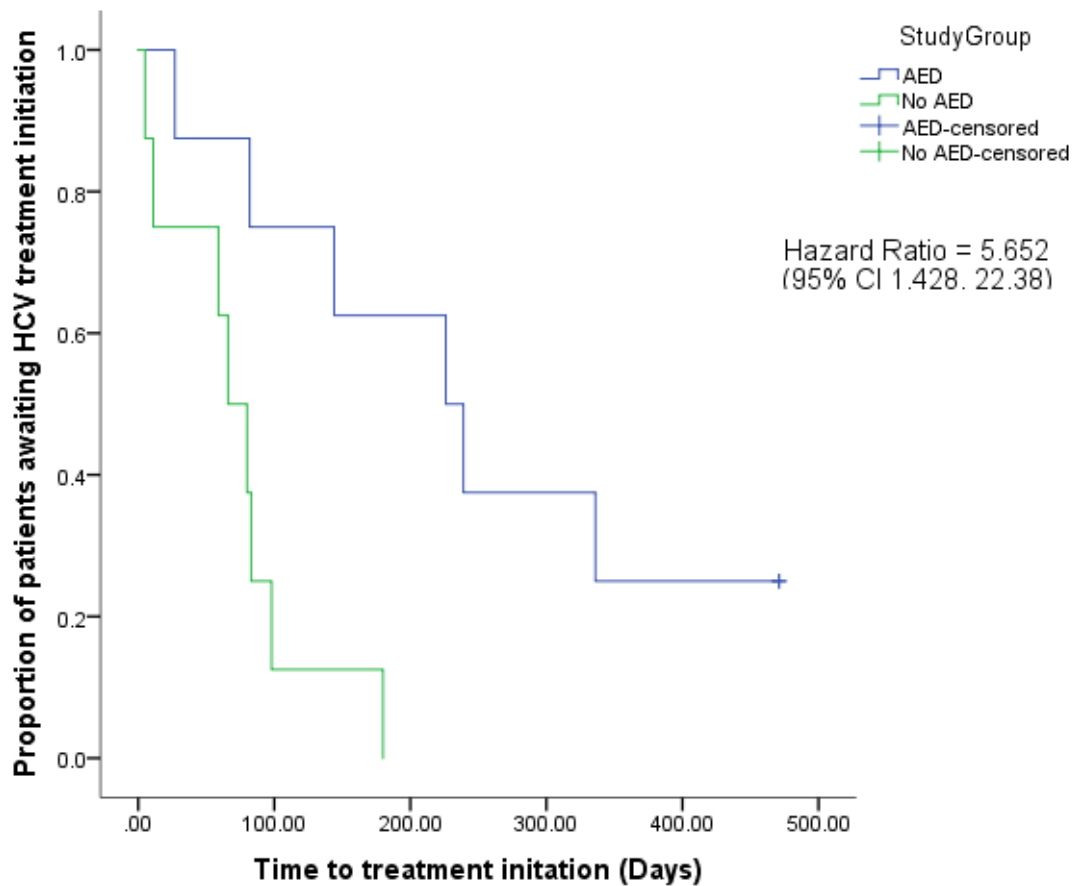


Figure 2.18 Time to Hepatitis C treatment initiation between study patients receiving antiepileptic medication for epilepsy which was contraindicated with HCV direct acting anti-viral therapy and a matched control group of patients not prescribed AEDs.

Patient outcomes

Two patients within the AED study group have been unable to initiate HCV therapy to date due to ongoing DDI issues with AED regimens. Both patients are under the care of neurology and hepatology specialists. Among the twenty epilepsy patients whom have initiated HCV DAA therapy to date, all have completed treatment and achieved a sustained virological response. No patient discontinued treatment and no seizure episodes were reported during treatment in the AED group.

Limitations of this study

The small number of patients eligible for inclusion and the retrospective design of the study.

2.3.4. Key Findings:

What was known prior to this study?

- AEDs are associated with more DDIs than any other class of medications.
- No data available on real-world management strategies of DDIs between DAAs and AEDs.

What is the added value of this study?

- Study findings suggest a high rate of clinically significant DDIs between DAAs and AEDs in patients with epilepsy in a real-world setting.
- Management of DDIs is impacting on the time to initiation of HCV treatment for patients prescribed enzyme inducing AEDs including phenobarbital, carbamazepine and its derivatives.
- The challenge of DDIs will continue to be part of the HCV treatment process for patients with epilepsy in the future, as newly licensed regimens display a similar pharmacokinetic profile to those prescribed in this analysis.

Implications of the new findings?

- A need was identified for a rapid neurology referral pathway and this is now in place.

Conclusions of Phase 1 of this research and implications for optimising HCV treatment outcomes

What was known

- The Hepatitis C model of care has and continues to rapidly evolve in Ireland and worldwide.
- The standards and quality of care must be maintained.

What the research has added

- Pharmacist-led interventions included medication reconciliation and DDI identification and management are key roles in the stewardship of DAAs to ensure optimum patient outcomes.

Implications

- Involving non-specialist HCV healthcare providers is the next step.
- Regardless of treatment setting, patients must be able to engage with healthcare providers with treatment knowledge and adequate resources to ensure evaluation for & initiation on the optimum treatment regimen.

Chapter 3: Complex intervention design, development, optimisation, evaluation and implementation

3.1. Introduction

Initial UK MRC guidance stated that “the greater the difficulty in defining precisely what are the “active ingredients” of an intervention and how they relate to each other, the greater the likelihood that you are dealing with a complex intervention” (258). They often involve multicomponent interventions with dynamic interactions between several evolving organisations or groupings that act both independently and interdependently (259, 260). Interactions between intervention components and their effects on outcomes are not always linear or obvious, and they may be influenced by multiple factors (260).

In addition, complex interventions may involve systems with feedback mechanisms, so that the results of some actions can have widespread effects across the entire system and not just at one specific point. Complex interventions can also be adaptive with individuals involved in the process displaying variable behaviours based on their environment. Beehives are a commonly used example of complex systems, as understanding how a single bee survives will only go so far as to understanding how a bee colony operates.

More recently it has been acknowledged that not all intervention complexity may lie in an intervention’s components (261). There are several potential reasons to consider an intervention complex. It may be due to the range of possible outcomes of the intervention, or their variability of use by the target population, rather than with the number of steps in the intervention itself (261). There is no defined cut-off between what is considered a simple or complex intervention. Therefore, few interventions are in reality simple, but there is a wide range of complexity (262). For example, complexities may be encountered around behavioural changes required among a

healthcare team utilising an intervention, the context in which an intervention is implemented or where an intervention required involvement from staff members at multiple different positions within or among organisations (259, 260). In summary, complex systems behave in a way that is greater than the sum of their individual parts. This means that you can't understand the system just by looking at its individual elements, but rather it has to be studied as a whole.

Healthcare settings such as general practice, addiction service clinics and hospital inpatient and outpatient units are examples of complex systems. Their functioning is shaped by continually changing interactions between multiple factors including healthcare staff, patients, medical and surgical procedures and service capacity (259). Healthcare systems must continually adapt to ensure service provision is continued at a level which meets the public need. Complex systems also tend to display unpredictable patterns of system behaviour in response to the introduction of change at any step in the work process (259).

Complex intervention tools facilitate HCPs in making clinical decisions related to patient care. Development and implementation of clinical intervention tools has been described in multiple healthcare states with prior research highlighting their positive impact on consistent care standards, lower healthcare costs, and outcomes of care (187).

3.2. Complex intervention design and development

Research within the area of complex interventions and their design is a new development in healthcare over the last two decades. A range of different guidelines or frameworks for the development and evaluation of complex interventions are described in the literature (260, 262-266).

Campbell *et al* published an initial guiding document for complex intervention development from the MRC in the UK in 2000 which was later updated in 2008 (262, 267). Initially, this framework followed a five phase, linear approach. This has subsequently been updated to be more flexible, reflecting that research on the context, the intervention and the evaluation may be conducted simultaneously rather than sequentially. In the revised framework, the development stage aims to gain an understanding of the problem, the intervention and the evaluation. Both feasibility testing and piloting are used to identify key uncertainties of the study design prior to the full randomised control trial (RCT) such as feasibility and acceptability, face and content validity testing, pilot testing and delivery of the intervention. The development and evaluation of complex healthcare interventions requires a systematic, stepwise approach giving consideration to how the intervention will interact with the environment in which it is intended for use, how it will be received by HCPs who will utilise the resource and how it will therefore impact patients involved in the specific healthcare system (259, 262, 267). The UK MRC framework for the development and evaluation of complex interventions in healthcare is a widely cited guide to the process of complex intervention research and design (Figure 3.1) (261, 262, 267).

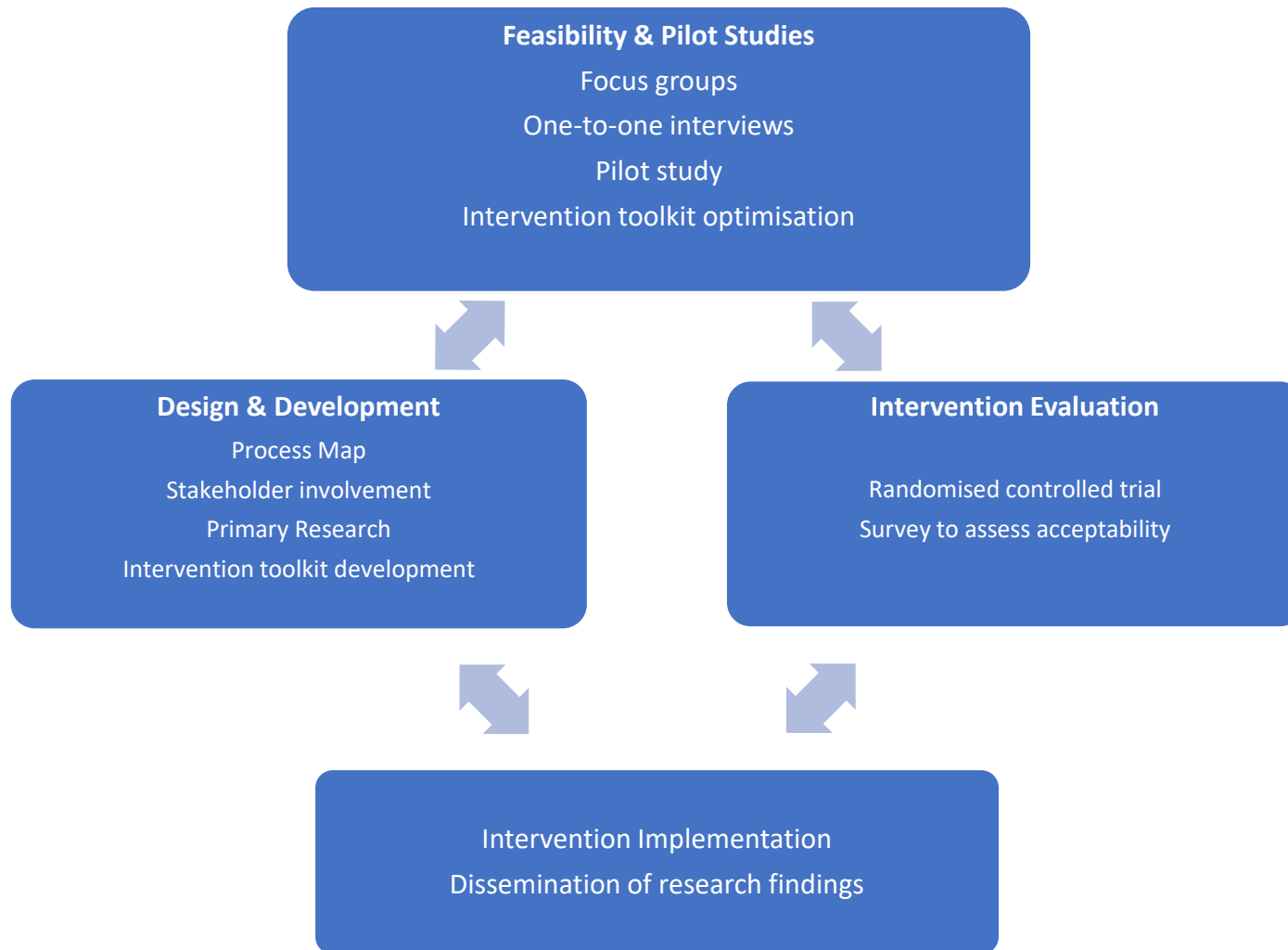


Figure 3.1 Medical Research Council Complex Intervention Development and Evaluation Process

Collins *et al* developed and published the multiphase optimisation strategy (MOST) framework, a strategy for developing and optimising behaviour interventions (266). While the MOST framework is based on some of the same theories proposed by the MRC, it draws more attention to the importance of optimising complex interventions which is an important component of complex intervention development which has come to the fore in recent years in terms of its importance (266). The MOST framework consists of three phases (266). First a screening phase where multiple small studies are completed to select the potentially important components of an intervention. Then, the next refining phase, the interactions between the selected intervention components and their inter-relationships with other system variables are studied (266). Finally the confirming phase sees the results of the screening and refining phases combined to build an optimum intervention (266).

Normalisation process theory, provides a set of sociological tools to understand and explain the processes through which new or modified practices of thinking, undertaking to complete, and organising work are implemented, embedded, and integrated in healthcare and other organisational settings (264). Some published research studies developed their own guidelines for complex intervention design and development.

These guidelines and frameworks acknowledge the key requirement to limit sub-optimal intervention design and implementation failure. As such, they all emphasise the importance of testing the intervention's potential effect and evaluating how interventions work before embarking on a full-scale randomised controlled trial.

However, existing frameworks differ in the language and terminology used, and there is a lack of clarity over the specific purpose and scope of each proposed stage of work to be conducted before full-scale RCT evaluation. In addition, the different guidelines and frameworks propose a range of

methods to achieve optimal intervention design and evaluation. Evidence to support the use of these methods for particular purposes is lacking, and there is limited guidance on the specific detail of how to plan and design optimisation studies. This leads to confusion about which guideline or framework to follow and which optimisation strategy is likely to be most suitable for the different types of intervention under evaluation (260).

The entire process of complex intervention toolkit development is dynamic, with refinements and alterations to the intervention content and mode of delivery needed on an on-going basis as toolkit development transitions between initial design and development to pilot and feasibility testing prior to the final trial evaluation phase (262). The process from development through to implementation of a complex intervention can take a variety of different forms (262). However, what is important is that interventions are developed using the best available evidence and appropriate theory (262, 268). Although it is useful to think in terms of stages, it is important to understand that often the stages will not follow a linear or even a cyclical sequence. Reporting and dissemination of the outcomes of each phase of complex intervention tool is also an important element of the design process (262). This research project will focus on the widely cited and utilised MRC guidelines as a basis for complex intervention design, development and evaluation (262, 267)

3.2.1. Phase 1: Identify the evidence base and theory behind the intervention

This first step in the complex intervention design process involves developing a sufficient understanding of the problem at hand, to identify opportunities for intervention that could result in meaningful improvements in health or healthcare systems (258). A range of research methods can be used to collect evidence including literature review, epidemiological research, gaining expert opinion and completion of primary research to quantify the extent of the problem and the potentially modifiable risks. Qualitative research can explore opportunities for, and barriers to, change. The findings of these research method, and extrapolations from other related research, can inform an initial assessment of how much improvement the intervention is likely to achieve (258).

The number and types of potential intervention outcomes must also be considered. Does the process of the intervention change or adapt depending on the location where the intervention is undertaken or completed? What are the aims of use of the intervention in question and what is hoped to be achieved by its implementation? Many interventions are poorly theorised and their mechanisms are unclear. It is vital to have a good theoretical understanding of how the planned intervention causes change, and to gain a full understanding of all of the potential outcomes (good and bad) so that any weak links in the complex intervention pathway can be identified and strengthened (258).

Complex interventions may be aimed at three different levels within an organisation, the individual level (e.g. patients , health policy makers, HCPs), at community groupings (e.g. hospitals, schools, GP practices, community nursing units) or at an entire population level or multiple levels (262). If an intervention is seeking to achieve change at more than one level, then processes and outcomes also need to be measured at each level (262).

It is an important early task in the development of any intervention to consult with all relevant stakeholders (e.g. those involved in its development or delivery). Stakeholder consultation is important throughout, particularly at the early stages as this will help to identify potentially unforeseen barriers to complex intervention implementation or uptake. Barriers can be cognitive, behavioural, organisational, due to social or cultural issues, or financial constraints. Barriers may occur early in the intervention process or during steps not previously considered or thought important. Early identification of any potential implementation barrier provides opportunities for resolution.

3.2.2. Complex intervention modelling

Logic modelling or mapping can help to clarify the mechanisms by which an intervention might achieve its aims. It is a visual depiction of the proposed intervention. This process involves mapping out the mechanisms and pathways proposed that lead from the intervention to the desired outcomes. Modelling of the intervention informs our understanding of the underlying problem. A logic model considers intervention inputs, activities that resource these inputs, mechanisms that these inputs activate and their resultant outcomes and impacts, short and long term (269).

The logic model can also help to expose weak links or potential problems in the intervention. It can identify where stakeholders have differing understandings of the intended intervention and outcomes. It can help with resource and timeline planning for the overall project. It can also help to identify when context (e.g. use of a complex intervention across multiple healthcare settings with different resources) and implementation may impact or alter intervention outcomes. An example of a logic model format is the Kellogg Foundation Model (269). It allows a shared understanding of the intervention and process among the research team. Modelling, like stakeholder engagement can also help to identify barriers to complex intervention implementation or uptake. The Kellogg Foundation Model is an example of a theory approach logic model. Other

types of logic model include outcomes approach, activities approach and research performance logic models.

Different health problems have different levels of complexity. Some can be conceptualised and modelled in relatively simple ways, but others occur at multiple levels. A logic model can include multiple factors including geography, epidemiology, social and cultural influences, political and legal considerations and ethics relevant to the intervention. For example, Table 3.1 describes factors which may impact mortality among people with liver cirrhosis.

Table 3.1 Factors which may impact mortality among people with liver cirrhosis

Disease factors	Non-alcohol related steatohepatitis, non-alcohol related fatty liver disease, HCC, autoimmune hepatitis and viral hepatitis.
Additional risk factors	Excess alcohol consumption, drug-induced liver injury, obesity, lack of exercise and injecting drug use
Co-morbidities	Diabetes, obesity, metabolic disorders, fatty liver disease, HIV co-infection.
Patient factors	Beliefs about lifestyle, on-going drug use, on-going risk behaviours risks associated with acquiring viral hepatitis, issues with compliance with medication and diet restrictions put in place to manage liver disease, requirement to attend regular hospital/GP/addiction services/community pharmacy appointments and symptoms of liver cirrhosis.
Healthcare practitioner factors	Accessibility, prescribing practices, practices in health promotion.
Health service factors	Availability of effective preventive and therapeutic care.
Policy factors	Policies on preventive services (alcohol education, detox services, availability of addiction services, diet and exercise advice).
Social context factors	Socioeconomic status, social support, literacy.

3.2.3. Initial complex intervention toolkit design and development

Core components of a complex intervention should be standardised during the development process. Following on from theoretical and logic modelling, complex intervention design must then go through several specific stages including content and face validity assessment, piloting and testing the feasibility of the intervention and evaluation of the impact of the complex intervention using an experimental design (270).

3.2.4. Stakeholder involvement

As previously stated, appropriate stakeholders should be involved at all stages of the development process and outcome analysis of a complex intervention, as this is likely to result in a better, more relevant intervention tool with a higher chance of being successfully implemented in practice. This may come in the form of focus group participation, one to one meetings or completion of questionnaires. Qualitative research, as well as providing important insights into processes of change, can be a good way to involve users. It can complement user involvement in steering groups, and allows for a wider range of views to be captured and systematically incorporated into the design of an evaluation (262).

3.3. Methods Phase 1: Development of the complex intervention

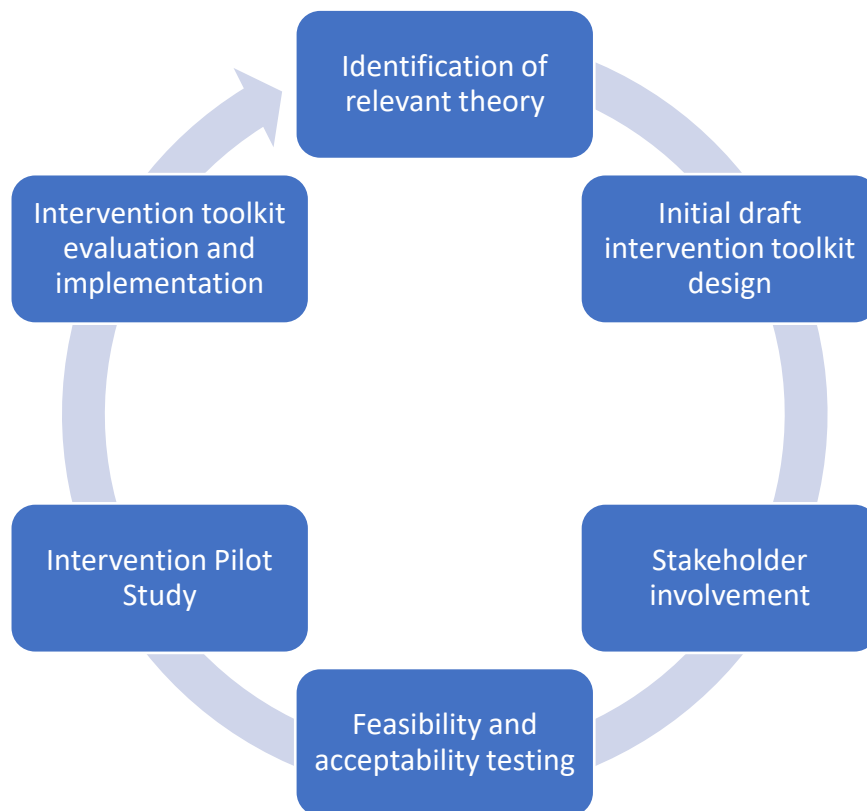


Figure 3.2 Complex intervention toolkit development framework

Study Objectives

- To explore the theoretical and real-world evidence available relating to the pharmacist-led interventions in Hepatitis C patient care and parallel pharmacist roles in other disease states.
- To identify existing literature around use of complex interventions in healthcare, pharmacist-led care and where available in Hepatitis C patient care.
- To develop a process map of pharmacist-led interventions in HCV patient care.
- To identify key pharmacist-led interventions for inclusion in the pre-treatment assessment complex intervention toolkit.
- To describe the design, development and optimisation of a novel complex intervention toolkit.

- To refine the understanding of how the intervention works and facilitate ongoing adaptation of intervention and evaluation design in preparation for a full evaluation.

3.3.1. Phase 1 Method 1: Literature review to identify the evidence base

A range of research methods can be used to collect evidence including literature review, epidemiological research, gaining expert opinion and completion of primary research to quantify the extent of the problem and identify the groups most at risk and the key modifiable risks. A literature search strategy was designed. Key words used to capture relevant research were identified (Table 3.2). Studies describing, investigating and measuring the effects of pharmacist-led activities in the care of patients with HCV were considered for inclusion. Because of the limited amount of research identified in this area, the literature search was broadened to include parallel pharmacist roles in other disease states. A separate literature review was also completed to identify research into the development of complex interventions in a healthcare setting.

The research databases PubMed, Science Direct and Embase were utilised in this search strategy. Combinations of MeSH terms and keywords were utilised, including healthcare, hepatitis C, intervention, pharmacist, complex, patient, algorithms, decision-support systems and model of care. (Table 3.2). Further publications were identified by a manual search of the reference lists of relevant studies already identified. No time limits were applied to the database searches, however, articles included in review were limited to English language full text only. Conference abstract were also considered for inclusion. Publication alerts were created for the literature review search terms using the Embase database to aid the process of on-going literature review. Exclusion criteria included articles not in English and where full text of the research publication were not accessible.

Table 3.2 MeSH terms and keywords

MeSH terms and keywords	
Hepatitis C	Complex intervention
Healthcare interventions	Pharmacist
Decision-support systems	Medication therapy management
Model of care	Drug-interaction
Patient safety	Medication compliance
Algorithms	Pharmacist medication reconciliation
Clinical pharmacist/pharmacy	Patient care
Health education	Patient education
Outpatient care	

3.3.2. Phase 1 Method 2: Primary Research

The importance of both medication reconciliation and DDI review, as part of the complex intervention process of patient assessment for HCV treatment, were assessed separately via primary research projects, to examine their clinical impact (Chapter 2).

3.3.3. Phase 1 Method 3: Complex intervention toolkit modelling and initial draft design

Process Mapping

An in-depth process review of the pharmaceutical care pathway of HCV patients at outpatient clinics in St. James's Hospital was undertaken from January to March 2016. A workflow chart of current clinical pharmacist activity in the Hepatology and Infectious Diseases clinics was completed by the pharmacists working within the units. Pharmaceutical care tasks completed during the HCV patient care process were described qualitatively by the lead researcher and formed the basis for the initial complex intervention toolkit. The process map was then reviewed by three other pharmacists working within the Department of Genito Urinary Medicine and Infectious Disease (GUIDe) outpatient department at St. James's Hospital.

Stakeholder Research Group

A research working group comprising representatives from all relevant stakeholder groups

(pharmacists, nursing staff, medical staff and healthcare researchers) was established. Members were recruited from all groups involved in the care of HCV patients. These included clinical nurse specialists, Hepatology and Infectious Diseases physicians, clinical pharmacists, specialist GPs and addiction service healthcare professionals. Members were contacted by email and phone to request their participation in the working group. A short summary of the project outline and aims was provided.

The role of the stakeholder research group within the design and development of the complex intervention was advisory in terms of the initial design and development stages. The research group agreed on a set of initial guiding principles to be considered as part of the complex intervention toolkit design and development. The lead researcher used their specialist knowledge in the area of HCV DAA therapy coupled with information gathered through the literature review to design an initial draft intervention toolkit incorporating the key processes identified during the process mapping phase of the study.

The research group were also asked to review the format of the complex intervention toolkit at set time points during its development and also to complete a last review once the final toolkit format and design had been decided. Research group members were permitted to suggest additions or alterations to the complex intervention toolkit draft design. The research group employed a consensus type methodology. The layout and content within the complex intervention toolkit were revised during each review to incorporate feedback from the research group.

Research group members were asked to give their opinions on:

- What are the key processes and outcomes of this complex intervention being designed?
- Organisational motivations that may impact the adoption of the novel complex intervention toolkit into HCV patient care in Ireland across all models of care (e.g. hospital outpatient clinic, addiction services, community-based GPs and pharmacies).

- Identification of potential barriers or facilitators to the implementation of the intervention.
- The best achievable combination of intervention components and intensities.
- Contextual factors that may impact the outcome of the novel complex intervention toolkit in practice.
- The user friendliness and readability of the toolkit. This is a key assessment as a good tool may not be used because it is hard to navigate or too lengthy or perceived as an increase in workload.

These questions were posed to stakeholders via email and also in face to face meetings.

Development of a logic model

A logic model was developed and used to clarify the mechanisms by which the intervention aimed to achieve the outcome of optimum HCV DAA regimen selection. The logic model was also designed to increase understanding of the intervention plan among the stakeholder research group participants and to identify necessary resources and inputs required for successful implementation of the intervention toolkit.

Findings from the literature search were combined with data gathered through the research group meetings and process mapping. The Kellogg model for logic model development was employed (269). The logic model utilised 5 domains (Figure 3.3). Antecedent system influences refer to what current practice looks like and how people perceive problems relating to current practice. Resources required is the tools we need to help to achieve our study aims. Activities are the list of specific studies being completed to assess the novel complex intervention toolkit. Outputs of the complex intervention toolkit studies which will guide future development and implementation of the toolkit. Outcomes and impact are the expected results of toolkit use in the short (1-2 years) to long term (5-10 years).

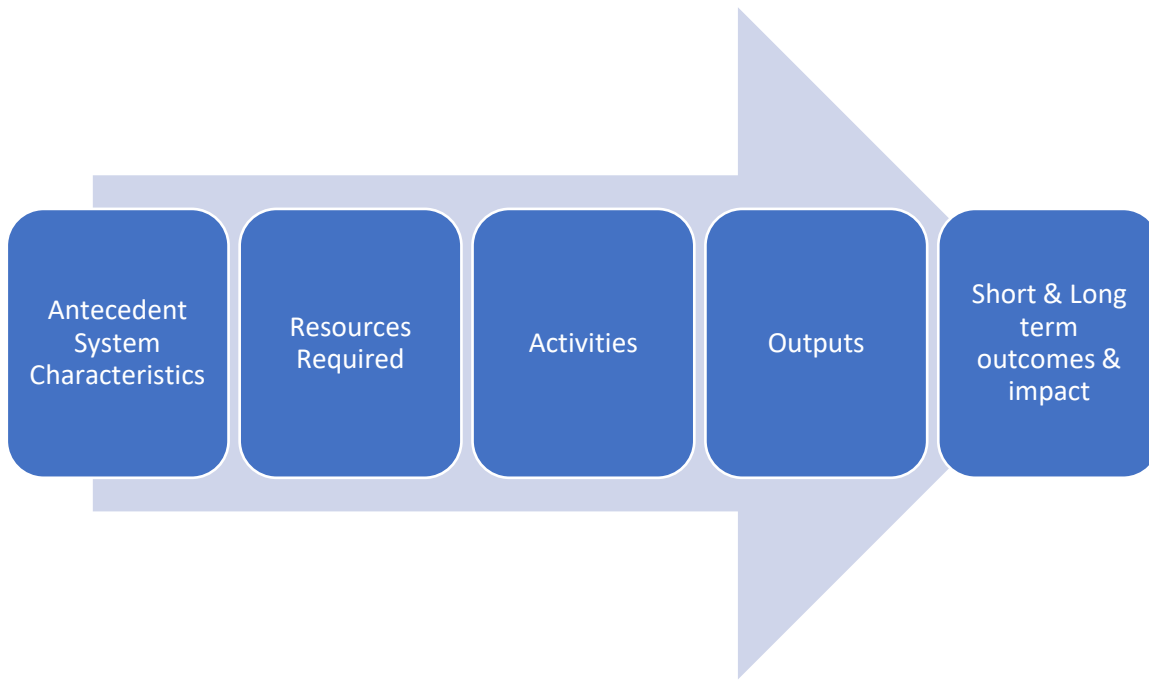


Figure 3.3 Logic model domains (269)

3.4. Results: Phase 1: Development of the complex intervention

3.4.1. Complex intervention toolkit modelling and initial draft design

Process Mapping

The process review identified five specific pharmacist-led interventions which occur prior to HCV treatment initiation. This process review gave the initial structure and task order to the complex intervention toolkit design and development (Figure 3.4).

The key processes identified by the process review were:

1. Baseline patient characteristics review
2. Medication reconciliation
3. Review of the potential HCV treatment regimen options
4. DDI review
5. DDI report and summary presentation to the MDT. Outcomes of the MDT and agreement of a DDI management plan

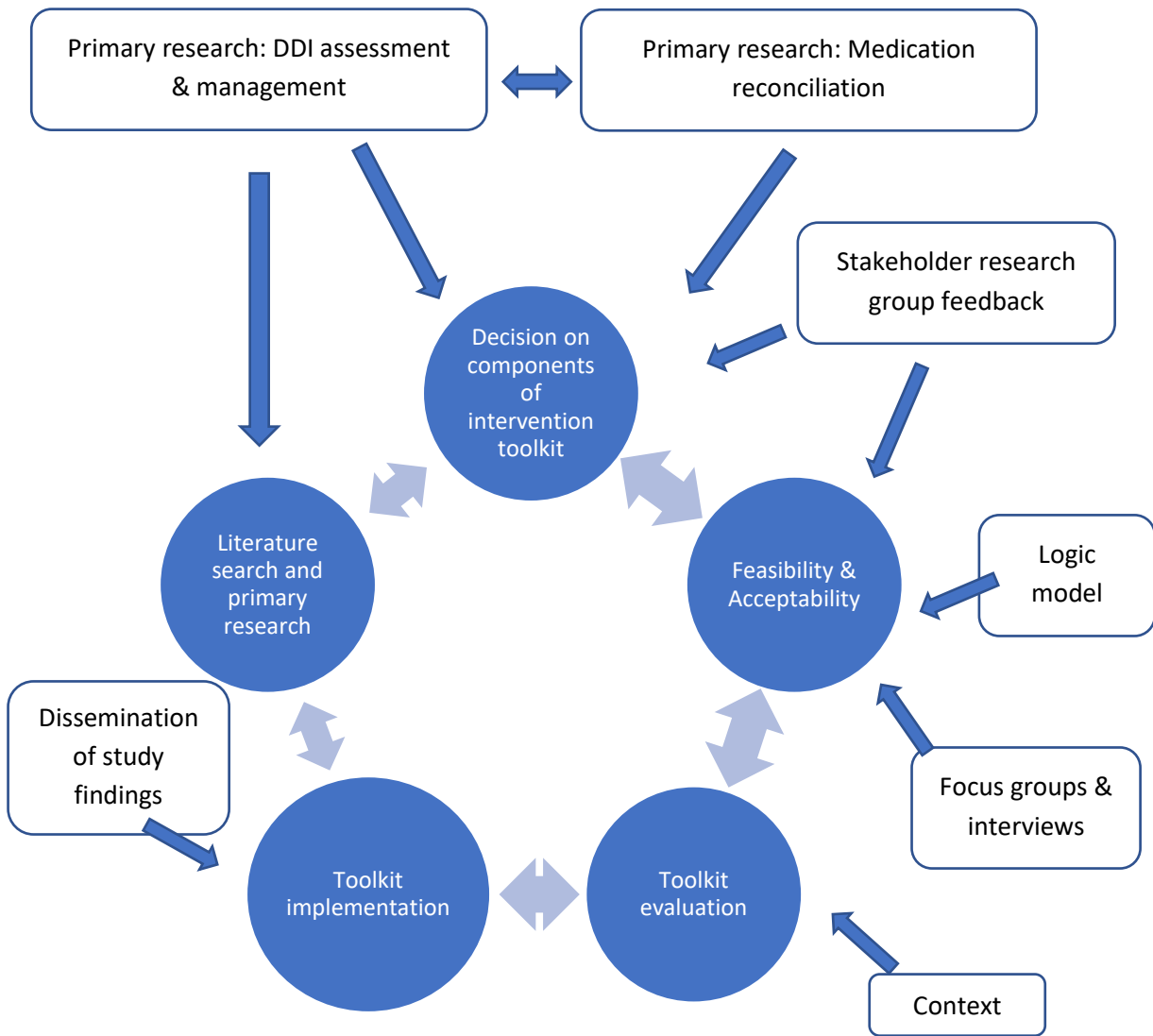


Figure 3.4 The pre-treatment patient assessment complex intervention toolkit design process

Formation of a Stakeholder Research Group

The stakeholder research group agreed on a set of initial criteria/guiding principles to be considered as part of the complex intervention toolkit design and development process:

1. The toolkit should capture all common & important potential points of error along the HCV treatment assessment and regimen selection pathway.
2. Toolkit format should flow chronologically.
3. The toolkit should highlight/place special emphasis on high risk patient groups. e.g. patients with cirrhosis, multiple co-morbidities and/or co-medications
4. The toolkit should help to capture and highlight any medication reconciliation or DDI issues.

The lead researcher used their specialist knowledge in the area of DAA HCV therapy management and the process map to design an initial draft intervention toolkit incorporating the key processes and principles identified during the process mapping and criteria development phases of the study. Toolkit design began in a checklist format. This was then adjusted to a tabular format and circulated to the research group for the beginning of the review and refinement process with the aim of optimising the draft complex intervention toolkit prior to feasibility and pilot testing. (Appendix 25)

Nine iterations of the complex intervention toolkit were reviewed by the stakeholder group following the first draft of the qualitative review, resulting in a total of 35 recommendations and the proposal of 29 new additions or changes to the toolkit, of which 26 were accepted. Four discrete complex intervention toolkit domains were identified and developed, i.e. baseline patient characteristics, medication reconciliation, proposed HCV treatment regimen review and DDI recommendations. The evolution of the complex intervention toolkit is detailed in Appendix 25 along with any changes that were made at each revision step.

User friendliness and readability of the toolkit was a key assessment, as a good tool may not be used because it is hard to navigate or too lengthy or perceived as an increase in workload. This was completed during the review rounds by the stakeholder group and in the feasibility and acceptability focus groups and interviews.

3.4.2. Components of the PTPA complex intervention toolkit

The PTPA complex intervention toolkit developed involved components that follow a logical, practical process based on stakeholder feedback and primary research. Each section requires completion prior to progressing to the next section.

PTPA toolkit Part 1: Patient baseline characteristics:

Patient Age	yrs		Gender		
Patient Weight	kg		Date of weight		
Hepatitis C Genotype			HCV Viral Load		Date:
First Diagnosed			Route of acquisition		
Liver Disease Staging	Fibroscan: _____ kPa Date:		Biopsy: _____ Date:		Ultrasound/CT: _____ Date:
Co-morbidities					
Alcohol Intake					
Allergy Status					
Baseline Laboratory Markers	AST		ALT		Bilirubin
	Na ⁺		Platelets		Creatinine
Date of Labs:	Albumin		Gamma GT		Alpha-feto protein
	INR		Dialysis	Y/N	Haemoglobin
Renal Function	Cockcroft & Gault				Date
Hepatitis B Markers	Core Antibody				Surface Antibody
	Surface Antigen				HBV viral load
	Hepatitis B e Antigen (If HBV infection confirmed)		e Antigen positive		e Antigen negative
HIV Ag/Ab Combo					

Figure 3.5 PTPA toolkit baseline patient characteristics

Rationale for inclusion: This section serves as a checklist for all patient demographic and clinical parameters required by the intervention toolkit user to assess the appropriateness and safety of any subsequent HCV therapy prescribed (Figure 3.5). It forms the basis of a picture of the patient in terms of liver health and overall health status at that point in time.

The toolkit user is then required to use the baseline characteristics information gathered to determine the stage of liver disease of the selected patient and if the patient has liver cirrhosis as

this will impact HCV treatment plan and also the long-term liver care plan. It consists of the following factors:

- Patient age
- Patient gender
- Patient weight (date checked): Knowledge of patient weight is important to allow calculation of creatinine clearance. Monitoring of patient weight is also important in the monitoring of patients with decompensated cirrhosis and in determining the appropriate dose of RBV, if required.
- HCV genotype and viral load (date of sample): This dictates DAA treatment options and duration of treatment for specific regimens (e.g. 8 weeks SOF/LDV in genotype 1 treatment naïve patients with a low viral load). The date of the viral load sample and the interval between positive HCV viral load results is important in terms of confirming the presence of chronic infection. Chronic infection is determined by two positive HCV viral load results, six months apart. Given that approximately 20% of patients will self-clear HCV in the acute phase it is important to ascertain this information.
- Time of first diagnosis
- Route of acquisition: This will impact patient counselling in terms of re-infection risk.
- Liver disease staging systems (Date staging completed). Accurate staging of liver disease is required to ensure optimum selection of HCV treatment regimen.
 - Fibroscan (kPa): >12.5kPa considered as evidence of cirrhosis. A lower threshold for cirrhosis suspicion was utilised in patients with HIV co-infection (>10kPa).
 - Liver biopsy (Ishak reporting system used)
 - Liver ultrasound: HCC surveillance
- Co-morbidities: It is important to be aware of all patient co-morbidities as they may impact the HCV treatment plan. For example, a patient with a history of poorly controlled bipolar depression may require greater clinical nurse specialist support through treatment, in the form

of more frequent clinic reviews.

- Alcohol intake (units per week): It is important to be aware of current alcohol intake in order to engage patients in appropriate alcohol reduction programmes and strategies while also ensuring that alcohol intake is not hindering patient compliance with DAA therapy. For some patients, this may mean use of compliance aids and increased patient reviews during treatment.
- Allergy status: Confirm the patient's allergy status and ensure that it is documented in the patient's medical notes. This is an important part of a patient medication history that is often missing from patient records. In the medication reconciliation study completed as part of this research project only 54% of patients were found to have their allergy history accurately documented in the medical records. Information about allergies is important in the setting of medication changes to overcome DDIs and prescribing of medications to management DAA related side effects.
- Baseline laboratory markers (date of sample)

The laboratory markers requested as part of the toolkit are those which are necessary to complete an assessment of liver function and to calculate specific liver health scores (Table 3.3).

Table 3.3 Baseline laboratory markers to assess liver function

Aspartate aminotransferase (AST)	Gamma-glutamyl transferase (GGT)
Alanine aminotransferase (ALT)	International normalised ration (INR)
Bilirubin	Sodium

- Haemoglobin: This is a key marker in the few patients for whom RBV is indicated. RBV is associated with significant anaemia as a side effect and monitoring haemoglobin helps to determine when RBV dose adjustments are required. The haemoglobin result at treatment assessment, together with patient weight will help to determine the starting RBV dose.
- Alpha fetoprotein: This a surveillance marker for HCC.
- Platelets: Low platelets can be a sign of portal hypertension, increased alcohol intake, illicit drug use or advance liver cirrhosis (decompensation).

- Renal function assessment:
 - Creatinine: This marker helps to determine patient renal function and is also a contributing factor to the model for end-stage liver disease (MELDNa) score calculation in patients with cirrhosis.
 - Dialysis: The requirement for dialysis by a patient is a contributing factor to the MELD score in patients with cirrhosis.
 - Creatinine clearance calculation using the Cockcroft and Gault equation (Date completed). This laboratory markers also allows the user to assess a patient's renal function prior to treatment to ensure it is sufficient to support use of specific DAA based HCV treatments.
 - G/P, grazoprevir/elbasvir and P/rOD are currently licensed for use in all stages of renal impairment, including in patients on dialysis. However, all other regimens are contra-indicated for use in patients with a creatinine clearance <30ml/minute (as per Cockcroft and Gault calculation).

- HBV status (date of sample): HBV virus infection reactivation, including some reported fatalities, has been recorded during or after HCV DAA therapy. A full HBV screen should be performed on all patients prior to initiation of DAA treatment. This consists of checking for core antibody, surface antigen, surface antibodies, HBV viral load and HCV eAntigen status (if confirmed HBV infection). HBV/HCV co-infected patients are at risk of HBV reactivation, and should, therefore, be monitored, managed and treat ed according to current HBV clinical guidelines (60, 61).

- HIV screen: Positive or negative (Date of sample): It is important to confirm HIV status in all patients prior to treatment initiation given that previous research tells us that one third of HIV positive patients are co-infected with HCV (224). Due to common routes of transmission, a significant proportion of HCV infected patients are also HIV positive and require lifelong treatment for this condition. HIV/HCV-coinfected patients experience more liver-related

morbidity and mortality, more rapid fibrosis progression, greater extrahepatic morbidity, and overall mortality than HCV mono-infected patients (61). Therefore, it is key that this patient group are identified and linked to appropriate HCV treatment services. While it is possible to treat both conditions simultaneously there are important patient safety factors to consider, including the significant potential risk of DDIs between anti-retrovirals and DAAs.

Staging of liver disease

The toolkit user is then required to use the information gathered to determine the stage of liver disease of the selected patient and if the patient has liver cirrhosis (Figure 3.6).

Based on the available information does this patient have cirrhosis? If yes, please complete below questions		Yes	No	Not determined
If cirrhotic, has this patient had an episode(s) of hepatic decompensation?		Yes	No	Not determined
Presence or history of ascites	Yes / No	Presence or history of encephalopathy		Yes / No
Presence or history of varices	Yes / No	Presence or history of portal HTN		Yes / No
Hepatic Function Measurement in patients	Child Pugh Score	MELD Score	FIB-4 Score	
Date:				

Figure 3.6 PTPA toolkit staging of liver disease

AST to platelet ratio index (APRI): The APRI score is an easy, non-invasive and low cost method to assess liver disease staging patients with chronic HCV infection (271).

FIB-4: The FIB-4 index is a simple formula to predict liver fibrosis based on the standard biochemical values (AST, ALT and platelet count) and age (272).

These liver disease staging formulas may be of particular use in settings where access to fibroscan is limited or unavailable. Initial drafts of the PTPA toolkit included the APRI score however during the timeline of this project, use of the FIB-4 score dominated in local clinical practice. Feedback from the stakeholder and research group request a change from APRI to FIB-4 in section 1.

If the selected patient has cirrhosis, based on fibroscan scoring, liver imaging or utilisation of the above scoring tools then the toolkit user must complete the next section containing different

calculations relating to hepatic function in patients with cirrhosis.

Child Pugh Score (CTP): The score takes into account INR, albumin, bilirubin, presence and size of ascites and presence and extent of encephalopathy in assessing the severity of liver dysfunction in all patients with liver cirrhosis (Table 3.4) (273).

Table 3.4 CTP Score

Parameter	Score		
	1 point	2 points	3 points
Ascites	None	Mild	Moderate or Severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (micromol/L) OR Bilirubin in Primary Biliary Cirrhosis (micromol/L)	<35 <70	35-50 70-170	>50 >170
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.8-2.3	>2.3

The sum of the five scores from the above table is used to assign a CTP grade of A, B or C to the patient's clinical condition at that point in time as per table below (Table 3.5).

Table 3.5 CTP score & CTP Grade

CTP grade	CTP Score	CTP Grade (Level of Cirrhosis)
A	5-6	Compensated
B	7-9	Decompensated
C	10-15	Decompensated

Decompensated cirrhosis is defined as the presence of ascites or hepatic encephalopathy or spontaneous bacterial peritonitis and/or CTP grade of B or C.

MELDNa is a reliable measure of mortality risk in patients with end-stage liver disease (274). The MELDNa scoring system uses a patient's results for serum bilirubin, creatinine, sodium and the INR to predict three-month survival (274). In patients with cirrhosis, an increasing MELDNa score is associated with increasing severity of hepatic dysfunction and increased three-month mortality risk (274). In addition to the initial MELDNa score, the change in MELDNa score over time can serve as a marker for deterioration in liver function (275). Completion of this score is important in patients with decompensated cirrhosis as part of the decision to treat process and also throughout treatment

Ascites & encephalopathy: Ascites and encephalopathy are both considered signs of decompensated cirrhosis. It is important that history of a previous episode of ascites or encephalopathy, or on-going presence of either condition is identified and appropriately managed in any patient being assessed for HCV treatment. These factors are incorporated into the CTP score.

Portal hypertension & varices: Portal hypertension occurs as fibrosis progresses towards liver cirrhosis. If unmanaged, this can lead to the development of oesophageal and gastric varices. Variceal bleeding secondary to portal hypertension remains one of the most severe and immediate life-threatening complications in patients with cirrhosis and constitutes the second most frequent decompensating event after ascites.

These scoring tools and assessments for signs of advanced liver disease aid the toolkit user in determining if cirrhosis is present and if so, whether the patient is in a compensated or decompensated state.

Identification of high-risk patients

A key guiding criterion of the PTPA toolkit is to capture any high-risk patients. Patients with decompensated cirrhosis, including those with ascites, encephalopathy, portal hypertension and varices are a high-risk group and decisions around treatment must be made on an individual patient basis. One key factor for patients with decompensated cirrhosis is the caution and ultimately contraindication for use of protease inhibitor containing DAA regimens in this grouping (60, 61). This factor means that if decompensated patients are to receive DAA treatment for HCV they are limited to two treatment regimen options, SOF/LDV or SOF/VEL with or without RBV depending on patient tolerability (60, 61).

Part 2: Medication reconciliation

This section of the PTPA toolkit allows identification of all medications in use by a patient in order to assess their potential for DDI with DAA therapy.

Rationale for inclusion: An accurate list of a patient's concomitant medications pre-HCV treatment is essential in order to identify:

- a) Any medication which may result in a clinically relevant DDIs with HCV therapy.
- b) Any medication which may be affected by a clinically relevant DDI with a component of HCV therapy.
- c) Any medications which are inappropriate for use in patients with liver impairment
- d) To identify patients at risk of non-compliance due to high co-medication pill burden or sporadic medication dispensing and collection from their community pharmacy service.

A complete list of all information collected as part of the medication reconciliation process should be documented in the patient medical notes either paper or electronic.

The format of this section of the complex intervention toolkit is intended to prompt the user to

consider all potential sources of concomitant medications and also to consider the different medicine formulations patients may use. A list of the ten most frequent medication sources as identified in the medication reconciliation study completed as part of this research was included in a check list format.

These were patient interview, patient’s own medication list, patient’s own medications, contact with a patient carer/relative, contact with the patient’s community pharmacy, contact with the patient’s addiction services clinic, contact with a patient’s general practitioner, a patient’s medical notes, other healthcare providers and any electronic patient records available. Toolkit users are also prompted to consider all medication forms: Oral medications, topical agents, transdermal patches, inhalers, eye drops, herbal teas etc. The medication list is then documented by medication source (Figure 3.7).

Information sources used to determine the patient’s current medications:					
Patient interview		Contact with Community Pharmacy		Patient hospital medical notes	
Patient’s own medication list		Contact with Drug Treatment Centre		Electronic patient records	
Patient’s own medications		Contact with GP		Other healthcare providers	
Contact with a patient carer/relative					

Figure 3.7 Medication History Source Checklist

The medication documentation list section also contains a column entitled, “potential for DDI”. This is intended as a rapid first look or check to identify any medications at high risk of DDI (Figure 3.8). (e.g. amiodarone, phenytoin or efavirenz).

Source	Medication List	Potential for DDI
Community pharmacy		
Drug treatment clinic		
Hospital Outpatient Clinic		
Health food Shop /Supermarket/Gym supplements		
Online		
Illicit		
Other		
Contraception planning for both patient and partner(s)		

Figure 3.8 Medication documentation section with rapid DDI review section

Part 3: Review of the patient’s HCV infection profile, prior treatment history and the proposed HCV treatment regimen

This section focuses on the patient’s HCV background and matches genotype, viral load and previous treatment outcomes with an appropriate DAA regimen as specified in national and international guidelines (13).

HCV Genotype		HCV VL		Date	
HCV Treatment History	Treatment naïve		Treatment experienced		
Previous treatment regimens					
Previous Treatment response	Relapse	Partial response to IFN/RBV	Null responder	Viral breakthrough on treatment	
If treatment experienced with DAAs please document resistance profile					
Proposed treatment regimen					
Is ribavirin co-prescribed?	Yes		No		
Proposed treatment duration	8 weeks		12 weeks		
	24 weeks		Other:		
Does the proposed treatment regimen meet National treatment guidelines?	Yes		No		

Figure 3.9 Selection of HCV treatment regimen

Information required to complete this section:

- HCV genotype and viral load (date of sample)
- HCV treatment history: Treatment naïve or treatment experienced
- Previous HCV treatment received
- Previous treatment response: Relapse, partial response to IFN and RBV, null responder to IFN and RBV and viral breakthrough on treatment.
- If the patient is DAA experience, DAA resistance test results are required.
- Proposed treatment regimen
- Is ribavirin required? Yes/No
- Proposed treatment duration: 8/12/16/24 weeks
- Does the proposed treatment regimen concur with National treatment guidelines? Yes/No.

Rationale for inclusion:

It is key that HCPs assessing patients for HCV treatment consider all factors when making a decision

about DAA treatment regimens. Failure to consider previous treatment with IFN/RBV may result in a patient being classified as treatment naïve and potentially receiving short course DAA therapy, which would be suboptimal in this case and related to a reduced chance of attaining SVR and the potential for emergence of resistance.

PTPA toolkit Part 4: Drug-drug interaction review

Rationale for inclusion: It is essential to assess potential for DDIs between DAAs and co-prescribed medicines needs to be assessed and managed prior to treatment. Results from a DDI study completed as part of this research project identified that nearly three quarters (71%) of patients prescribed a concomitant medication were subject to a potential DDI which required pharmacist intervention. This same study found that 7.3% of patients were subject to a DDI which had the potential to reduce DAA exposure and thus negatively impact on HCV treatment outcome.

The key factors to consider when reviewing medications for potential DDIs are:

- Severity of the potential drug interaction
- Medication indication and patient-related risk factors
- Manageability of the drug interaction
- Risk: benefit assessment

Method of DDI assessment using the toolkit:

- Using the reference resource list provided the toolkit user must check each concomitant medication for the potential to interact with the proposed HCV regimen or for the concomitant medication to be affected by the proposed HCV regimen. (Appendix 6) Information should be documented in part 4 of the PTPA toolkit as collected. (Figure 3.10)
- For all interactions checks where the potential for an interaction to occur is identified or is unknown, documentation of the action taken and any monitoring plan which is to be put in place in part 4 of the PTPA toolkit. (Figure 3.10)

- DDI report & summary: Provision of a summary of all relevant drug-drug interaction to the HCV therapy prescriber along with suggested management plans for these interactions.

Step 4: Drug-drug interaction review (See reference resource list)

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan

Outcomes of MDT report discussion and plan:

CIT completed by: _____ Date: _____

Figure 3.10 Part 4 PTPA Complex Intervention Toolkit

A fully completed PTPA toolkit using a sample case is located in appendix 26.

Reference resources for use with the complex intervention toolkit

The PTPA complex intervention toolkit is accompanied by a list of reference sources and glossary of terms to facilitate toolkit users in completing the PTPA process.

- The complex intervention toolkit incorporates several scoring tools (e.g. MELDNa score), disease classification systems (e.g. CTP Score for Liver Cirrhosis staging) and calculation tools (e.g. Cockcroft -Gault equation to estimate creatinine clearance). An information sheet providing the toolkit user with information on these scoring tools and classification systems was developed and provided.
- A list of recommended references for completion of a DDI profile was developed and provided.

(Appendix 6)

- A link to the current National HCV treatment guidelines was provided.
- A glossary of all terminology utilised in the complex intervention toolkit was also developed and provided.
- A Microsoft Excel® PowerPoint presentation was prepared and provided to toolkit users.

(Appendix 19)

3.4.3. Development of a logic model

A logic model was developed to aid understanding of the intervention toolkit plan among the stakeholder research group and to identify necessary resources and inputs required for implementation of the complex intervention toolkit. (Figure 4.11) The logic modelling also helped to clarify the mechanisms by which the intervention aimed to achieve optimised treatment uptake and efficacy and how the different components of the toolkit interacted.

Antecedent System Characteristics	Resources required	Activities	Outputs	Short & long-term outcomes
<p>Specialist skills relating to the use of DAAs to treat HCV are confined to hospital outpatient clinics in Ireland.</p> <p>Hard to reach patient populations including homeless persons and PWIDs struggle to actively engage with the hospital outpatient system.</p> <p>To achieve HCV eradication in Ireland, DAA treatment options should be available to all patients through a model of care which they have the ability to access and engage with.</p> <p>Expanding the current model of care requires investment in evidence-based interventions which can aid HCPs in the provision of HCV therapy to patients in the primary care setting.</p>	<p>Healthcare staff time</p> <p>Access to a room to complete workshop sessions, focus groups, interviews and training presentations.</p> <p>Design and development of the PTPA complex intervention toolkit.</p> <p>Development of a PTPA complex intervention toolkit training programme.</p>	<p>Completion of research meetings, focus groups and interviews with HCPs around feasibility and acceptability of the complex intervention toolkit.</p> <p>Training and education sessions completed with HCPs using a pre-designed complex intervention toolkit training resource.</p> <p>Provision of the PTPA complex intervention toolkit to study participants for use in the assessment of HCV patients for treatment.</p> <p>Identifying HCV PTPA complex intervention toolkit champions among the HCPs involved in the study.</p>	<p>A measure of the effectiveness of the PTPA toolkit at selecting the optimum DAA treatment regimen.</p> <p>Uptake rate and use of the PTPA complex intervention toolkit by HCPs in their assessment process for HCV patients.</p> <p>Qualitative assessment of HCP opinions on toolkit acceptability and implementability.</p>	<p>Measurement of the number of patients initiated on HCV therapy and treatment outcomes within the expanded model of care.</p> <p>Measurement of the number of HCPs involved in HCV patient care within the expanded model of care.</p> <p>A reduction in the prevalence and incidence rate of HCV infections in Ireland.</p> <p>Improved health outcomes for HCV patients in Ireland.</p> <p>Increased HCV knowledge and skill base among healthcare professionals</p>

Figure 3.11 Logic model for the PTPA complex intervention toolkit

3.5. Complex intervention toolkit Phase 2: Feasibility, acceptability and optimisation of the complex intervention toolkit

3.5.1. Phase 2: Optimising components of a complex intervention

Many complex intervention evaluation studies fail to show an intervention effect. Although this may be due to genuine lack of effect or impact, it may also be the result of sub-optimal intervention design, implementation failure or a combination of both. Optimisation is a process aimed to evaluate or test intervention components after the initial design phase, in order to identify what works and what does not, within the draft intervention format. The aim of the optimisation processes is to confirm the components of the intervention that are most likely to be effective if implemented in a full-scale evaluation. This process of optimisation is the least understood process related to the development of complex interventions (260). There is no consensus among research published to date, on how to achieve this. However, it is vital that all complex interventions in development undergo some form of optimisation process as good design is essential to get meaningful information from evaluation studies of complex interventions.

Key tasks in optimising a complex intervention (262):

- Identify key processes and outcomes of the intervention
- Identify mechanisms by which the intervention will lead to the proposed outcome.
- Identify potential barriers to implementation of the intervention
- Quantify the potential for benefit and estimate the likely effect size.
- Refine the target group to take account of its likelihood of responding to the intervention.
- Consider the best achievable combination of intervention components.

A scoping review by Levati *et al* classified optimisation strategies as prospective, in vivo or retrospective in nature (260).

- **Prospective optimisation strategies:** Prospective strategies explore theoretical perspectives and hypothetical intentions from different stakeholders in relation to the proposed intervention, presented through presentations and informative material.
- **Retrospective optimisation strategies** look for stakeholder feedback from those who have piloted the intervention in small, often uncontrolled, studies.
- **In vivo optimisation strategies,** look at implementation issues, in order to identify and apply potential changes to the draft intervention (260).

When retrospective and in vivo optimisation strategies are applied, stakeholders are involved in the piloting of the drafted intervention; thus, their feedback on feasibility and acceptability is informed by a 'real world' experience of the intervention in development. Whereas, prospective strategies allow stakeholders to influence from the outset rather than once the piloting is underway. This suggests that different strategies can be applied in different situations and for different purposes. Prospective strategies might be more appropriate in the design and development of the intervention, to help researchers identifying those components that increase the feasibility and acceptability of the intervention to the groups of people directly involved. Retrospective strategies might be helpful to gain confirmation of the potential effect of the intervention and its potential feasibility. Finally, in vivo strategies might be used in those situations where researchers are looking to implement changes during the pilot process to immediately verify how these influence the intervention effect (260).

3.5.2. Phase 2: Feasibility and Acceptability of the complex intervention

The acceptability of the intervention to those directly involved in the delivery and receipt of the final intervention, together with the anticipated effect of the intervention, are important elements to take into account as early as possible in the pre-evaluation stage. The feasibility and acceptability testing of a complex intervention includes testing procedures for their acceptability among potential intervention users. A mixture of qualitative and quantitative methods can be utilised, for

example, to understand barriers to participation and to estimate response rates for any potential full-scale evaluation. Qualitative methods which may be used include focus groups and one-to-one interviews. Interviews can help to provide context to other data and information gathered as part of the research process. One-to-one interviews are better for sensitive topics and are more private, allowing for more time to explore topics. These interviews can also yield more detailed answers. However, one-to-one interviews are associated with an increased monetary and time cost. Depending on the results of the pilot studies, further exploratory studies may be required to progressively refine the design, before embarking on a full-scale evaluation (262). Other strategies include observation studies or consensus processes involving relevant stakeholders and those involved in trialling the intervention. Several studies have employed well-established qualitative methods including interviews or focus groups with providers and recipients or relevant stakeholders and observations and consensus processes including researchers, patients and clinical experts (276-278).

For example, Radley *et al*, who examined the feasibility of directly observed HCV therapy in the community among patients receiving OST (104). This study identified factors that may influence uptake of HCV treatment including the presence of established relationships with pharmacy staff, a pre-existing reason for attending the pharmacy for OST and the proximity of the pharmacy to the patient (104).

3.5.3. Phase 2: Context

Context should be considered throughout the intervention optimisation process. Context includes anything external to the intervention that may act as a barrier or facilitator to its implementation, or its outcomes. An intervention may have different effects in different contexts even if its implementation does not change. Even where an intervention itself is relatively simple, its interaction with its context may still be highly complex (279). To have the greatest impact, effective

interventions should be combined and tailored for the specific population, location and setting where they will be in use.

Context needs to be accounted for across two dimensions, time and place. The healthcare setting is an open system of ongoing change and inherent variability. It is clear that in certain complex interventions, variations in the intervention design may be required from one context of use to another (for example in primary versus tertiary healthcare settings) (259). It must also be acknowledged that intervention effects are highly contingent on time (259). Time, meaning the risk factors associated with a problem that may evolve over time.

In addition, circumstances may change through the lifecycle of a study which may impact the context of use of the complex intervention. For example, the introduction of a change in healthcare policy or medication availability. It is important to develop a good understanding of the context in which the study is undertaken in order to assess the impact or effectiveness of an intervention carried out, and to monitor and document any significant changes (262).

3.6. Complex intervention toolkit Phase 2: Method

3.6.1. Phase 2: Feasibility and acceptability testing

Feasibility and acceptability testing involved an assessment of practicality of use of the newly designed intervention toolkit among HCPs in the HCV treatment setting. Factors asked about included issues around acceptability, implementation, practicality and use across different settings (context). This process also assessed face and content validity of the intervention toolkit. Content validity refers to the extent to which the PTPA complex intervention toolkit components considers all factors relevant to HCV treatment assessment. Face validity relates to whether focus group and interviews with potential toolkit users find it to be sensible, logical and relevant to practice.

A mixture of both one-to-one semi-structured interviews and focus groups were conducted to balance the potential pitfalls of use of a single qualitative assessment method. For example, use of focus groups alone may have helped to generate more open discussion around the intervention. However, it may also have caused a leaning towards consensus, masked participant true opinions or beliefs on a topic (social desirability bias) and limited the range of responses and opinions collected. There are also potential logistic challenges to co-ordinating meeting times and attendance of all focus group members. One-to-one interviews are the most commonly employed method of qualitative data collection and research. One-to-one interviews give the interviewee freedom and flexibility to develop and describe their opinions and ideas on the topics discussed.

The participants of both one-to-one semi-structured interviews and focus groups were provided with a draft version of the intervention toolkit during the feasibility and acceptability study. An intervention vignette was used as part of the qualitative interviews and focus groups to discuss step by step, the intervention with the participants.

A topic guide with a specific set of research questions was developed with questions linked to the research aims and intervention logic model (Appendix 13). Questions aimed to address key uncertainties surrounding the initial draft design of the pre-treatment patient assessment (PTPA) complex intervention toolkit, understanding of PTPA intervention toolkit use and identification of barriers or facilitators of PTPA toolkit implementation. Questions ranged in type from closed, yes/no questions to probing follow-on questions which aimed to elaborate and clarify participant views further. The “think aloud” interview method was employed and the topic guide allowed for the possibility of emergent questions.

Research Ethics Approval

Ethics approval was obtained from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (REC Reference Waiver of Ethics Approval 39/17. Date approved: 30/11/2017. (Appendix 14).

Eligibility criteria

Inclusion criteria: Participants of the feasibility and acceptability study had to be currently employed as a pharmacist, nurse or doctor and have experience working in the area of HCV patient care.

Exclusion criteria: No experience in the care of patients with HCV.

Recruitment

A diverse sample of HCPs working within the specialties of hepatology, infectious diseases and addiction services were recruited to participate in focus groups and interviews as part of this analysis. A purposive sampling method was utilised to ensure a wide sample of views were captured. A purposive sample implies that a researcher selects a sample of participants that is assumed to be representative of a particular population. Alternative sampling methods include random sampling, snowball sampling or clustered sampling.

Participants were invited to participate via email. The participation request email provided a study information leaflet which gave a brief description of the study background and its aims and objectives (Appendix 12). Further study information was provided as requested to potential focus group or interview participants. The initial study participation email provided the opportunity to refuse participation.

As the interviews and focus groups were subject to audio recording to facilitate accurate collation of study themes and findings, the study information leaflet discussed this and offered participants

the opportunity to refuse audio recording or to hear the recordings once the interview or focus group session had been completed. Informed consent was obtained by the researcher through email response to the study participation request email. Informed consent was obtained in line with best practice research guidelines and research ethics. Informed consent means that a patient is asked to participate in a specific study. They are given written and verbal information about the study and adequate time to ask questions and to consider whether they would like to participate. As part of this process they must be advised of their rights as a potential research participant that they can refuse or rescind consent at any time and that in the healthcare setting this will not impact their future care. If an individual who is approached to participate in a study, is willing to participate, they will be asked to sign a consent form. Implied consent is not best practice in research and means that a researcher assumes a patient is happy to participate without a patient expressly granting their consent and giving written confirmation of same.

Focus Groups

Four focus groups comprising representatives from all relevant stakeholder groups (pharmacists, nursing staff and medical staff) was established using a purposive sampling strategy. Focus groups allowed participants to engage in discussion with other group participants and to consider viewpoints that they may not have considered or been exposed to previously. Focus group members were permitted to make suggestions for addition or removal of components from the tool.

One to one interview

To maximise the amount of useful qualitative data collected, a semi-structured interview format was chosen for this study. One-to-one interviews were continued until data saturation was achieved. Interviewees were permitted to make suggestions for addition or removal of components from the tool.

Data Collection

All interviews and focus groups were recorded as digital audio files and transcribed in full, verbatim, for thematic analysis. Recording of the interviews rather than contemporaneous note taking was chosen as it permitted the researcher to engage more effectively with the interviewees and focus group members.

Data Analysis

Data was analysed as it was collected to facilitate learning from early findings to be implemented and incorporated into the on-going dynamic process of complex intervention optimisation. Data analysis aimed to identify recurrent themes within the collated data. Data was entered into Microsoft Excel® database. The feasibility and acceptability study dataset underwent a systematic quality control procedure according to van den Broeck *et al* to ensure the rigour to the results as data entry, particularly for the patient interviews may be subject to input errors (247). Therefore, a double data entry protocol was undertaken for a random 10% of the focus group and interview transcriptions to determine the extent of any errors. Once interview and focus recorded data that had been transcribed and had gone through this checking process, the original audio files were deleted to fully anonymise the study dataset. The cleaned database was then analysed. Data analysis was undertaken in St. James's Hospital by the primary investigator.

While there are computer assisted qualitative data analysis software packages available to analyse data, these programmes cannot replace the role of the researcher in interpreting the qualitative data collected. Narrative comments were analysed using a grounded theory approach to identify emerging patterns and themes. Analysis drew on the constant comparison method, operationalised within a general thematic approach. Collated themes and patterns identified were then interpreted in tandem with findings of the literature review, the process map and logic model developed and the stakeholder research group discussions.

Data management

Primary access to the anonymised feasibility and acceptability study results database was restricted to the primary investigators and co-investigators. Data is held on a secure server in St. James's Hospital. St. James's Hospital has strict data protection measures in place. Data held within the database is fully and irrevocably anonymised.

3.7. Results: Phase 2: Feasibility and optimisation

3.7.1. Feasibility & Acceptability of the complex intervention

Qualitative and quantitative research methods contributed to the refinement of the intervention through the use of focus groups and semi-structured interviews during the design and development phase. A mixed method approach was undertaken as part of the feasibility and piloting of the novel intervention toolkit to achieve optimisation prior to large scale evaluation of effectiveness. Double data entry checking for a random 10% of the interview and focus group notes and transcripts, identified four minor data entry errors for one interview and no errors in focus group data collation.

Roles of participants within the focus groups (N = 4 focus groups)

- Clinician: 8
- Clinical nurse specialist: 3
- Pharmacist: 6

One-to-one interviews (N = 4)

Roles of participants within the one-to-one interviews

- Clinician: 2
- Clinical nurse specialist: 1
- Pharmacist: 1

Demographics of feasibility study participants

The focus groups and interview participants represented a broad range of HCV experience levels ranging from two weeks to 12 years (Mean 4 years; Median 3 years; +/- S.D. 4.1 years). When asked to self-rate their knowledge in terms of HCV out of 10, with ten being excellent, there were a wide range of results from 1 to 9 (Mean: 5.6 Median: 6; S.D. +/- 2.3).

Healthcare professionals participating in this analysis reported involvement in a wide variety of HCV patient care activities including:

- Referral of patients to specialist HCV services and facilitating attendance to these services.
- Medical review of patients in specialist HCV services
- Prescribing DAAs and managing patients through HCV treatment
- Educating patients about HCV
- Medication dispensing
- Patient education and medication counselling
- Providing medication information
- Management of adverse effects
- Providing compliance support
- Providing inpatient HCV care services

Hepatitis C service provision challenges

Healthcare service provision challenges in terms of HCV patient care identified by participants included:

- Variation in practice among different treatment sites
- A lack of integrated care for a patient group which often have multiple complex needs.

- A lack of co-ordination among multiple agencies involved in patient management (including homeless services, prison services, housing services).
- The amount of time allotted to individual patient review in the clinic setting was a point noted by several participants as requiring review. The idea of longer patient appointment slots where services have the resource to provide this was seen as a method of enhancing patient and healthcare team relationships and subsequently improving the quality and durability of healthcare interventions provided.

Patient specific factors impacting HCV patient care

Patients factors which HCPs reported as challenging included complex patient cases, those who are harder to engage, due to chaotic lifestyle or prior healthcare or institutional experiences, and patients with on-going addiction. Participants reported that a lack of support services to address these uncertainties could leave to delays in HCV treatment initiation as they try to assess the correct treatment start point in terms of patient stability.

Solutions to perceived barriers to an expanded model of HCV care

Ideas or solutions presented by the participants included:

- Greater community supports and outreach of specialist services into the community
- Increased housing supports
- More integrated care services that co-ordinate between multiple service providers
- Provision of peer support services
- Making access to treatment more convenient for patients.
- The need to link treatment with established care links including opioid substitution, mental health and housing services was widely acknowledge by the participant group as a whole.

All interviewees acknowledged the need for treatment access to be devolved, through shared care, to the community among a variety of potential models, including co-location with addiction services and provision of treatment through homeless services. The main barriers they identified to this were funding, staff education, staff support systems and empowerment.

Use of complex interventions and scoring tools

All but one interviewee reported familiarity with, and use of, specific intervention tools in the everyday work including Q-risk score, CHADs score, training guideline algorithms and the STOPP START criteria. All agreed the intervention toolkits are beneficial in the healthcare setting. When questioned specifically into the potential role of a complex intervention toolkit to guide optimum treatment of HCV patients' participants felt that use of the toolkit would be beneficial. The most recurring theme in relation to this question was the potential for such a toolkit to increase staff confidence in terms of HCV treatment assessment completion.

Attitudes towards HCV PTPA

On review of the draft PTPA complex intervention toolkit and the associated supportive guidance documents, focus group and interview participants felt that the toolkit addressed many of their uncertainties or knowledge gaps in a standardised defined stepwise approach which would aid their completion of patient assessments for HCV treatment, while also providing them with education and learning.

- Participants reported knowledge gaps in relation to identification of DDIs with DAA regimens and selection of the optimum DAA regimen for individual patients.
- Another area where participants were reporting a need for further learning was around the cut off for cirrhosis diagnosis and the onward management of this patient type in terms of monitoring, management and follow up of their cirrhosis post HCV treatment. This is a key

section in the PTPA as participants also reported cirrhosis as the key patient factor in terms of being correctly identified and the need to treat HCV infection quickly and effectively.

- Participants also expressed uncertainty around which laboratory tests were required pre-treatment and how to manage scenarios of patients with poor venous access.

When the participants were provided with a copy of the PTPA complex intervention toolkit, specific feedback received included that it would be very helpful in a clinic setting for patient assessment and HCPs reported that it was an intervention they would definitely use in their practice. Interviewees stated that its availability as an electronic version to incorporate into electronic medical notes would add to its value. It was felt by two HCPs that it may be too long for use in some settings and therefore some adjustments made be needed if changing the context of the toolkit use.

When asked if they felt the PTPA complex intervention toolkit would be a beneficial addition to the HCV treatment model in Ireland, participants reported unanimously that they felt it would be of benefit. Some participants felt it was best directed at GPs or other new members of the HCV treating team. The possibility of its development into an electronic format was once again highlighted. One participant stated the idea of having the toolkit available on a community HCP online platform from where it could be downloaded for use as needed. When asked if they felt any HCP grouping in particular would benefit from use of a toolkit such as the PTPA complex intervention toolkit, participants responded that it could potentially be of use to any HCP and may work well as a support toolkit as part of the hub and spoke treatment site model or similar devolved care model. Respondents felt it would improve their assessment process by ensuring no questions or topics for discussion were forgotten or omitted thus requiring a further patient assessment review/visit.

In terms of the PTPA complex intervention toolkit having an impact on the number of patient assessments they complete for HCV treatment; respondents' feedback was mixed. One interviewee felt that in a devolved care setting the PTPA would increase the number of assessments they completed. One prescriber stated that making junior doctors aware of the toolkit may increase their awareness and knowledge of assessing inpatients for treatment. Other participants felt PTPA complex intervention toolkit use would definitely increase their confidence in completing assessments but could not be sure this would cause the rate at which they complete them to increase. Two interviewees stated that having the toolkit available may reduce the time to treatment start from the initial assessment visit.

Suggestions for inclusion within the PTPA toolkit

As the intervention toolkit is an on-going dynamic process, participants were provided with the opportunity to make suggestions for additions or removal of items from the PTPA complex intervention toolkit. All suggestions were discussed with the stakeholder research group.

Suggestions included:

- Development of an on-treatment guidance tool
- Addition of information relating to patient and partner contraception.
- A specific co-morbidity checklist
- Inclusion of OGD in the baseline characteristics section with information collected relating to date of last OGD if cirrhotic.
- Consideration of adding a list of the top ten most common DDIs to the toolkit.

Participant responses which captured the main themes within this qualitative analysis;

- *In relation to patients accessing HCV treatment, "It is not that they don't want to but they just have so many competing priorities".*

- *In relation to toolkit design and rationale, “The toolkit is great because it collates and disseminates this knowledge so that everyone caring for patients with HCV gets the benefit of it.”*
- *“Housing and addiction services cannot be forgotten; they must be combined into care of HCV and HIV. Housing as a health intervention, this is a piece we are missing.”*
- *“A great model of knowledge de-monopolisation”.*
- *“I would love to see this in other health conditions.”*
- *“I really think this will be useful and that it will benefit staff and patients.”*

Face and content validity testing resulted in changes to the complex intervention toolkit configuration, and the addition of two further questions to the complex intervention toolkit concerning HBV markers and DAA resistance. (Appendix 25)

Summary of key Findings:

- Study participants displayed a good understanding of the importance of the domains within the complex intervention toolkit and their impact on HCV treatment assessment, including medication reconciliation, proposed HCV treatment options, and DDI recommendations (Figure 3.12).
- Potential barriers to PTPA toolkit implementation identified included time and resource constraints.
- Focus group and interview participants demonstrated positive perceptions of the PTPA complex intervention toolkit
- Emergent participant questions identified further suggestions for toolkit optimisation.
- Implementation of the PTPA complex intervention toolkit was feasible and acceptable among all grades of healthcare professionals.

- Participants responded positively to the potential for the tool to contribute to staff education and to completion of patient HCV treatment assessments.

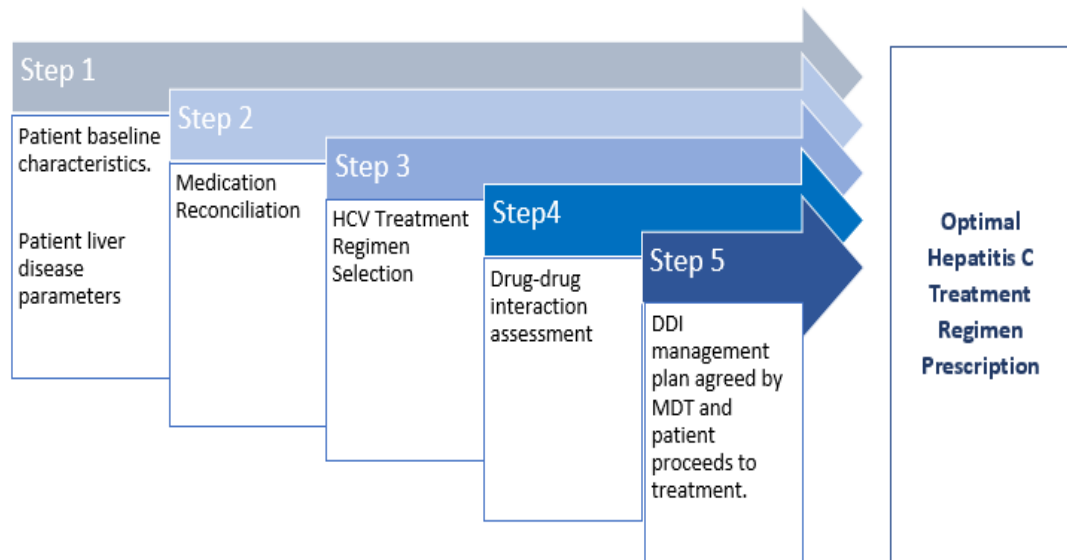


Figure 3.12 PTPA Intervention toolkit pathway

3.7.2. Phase 2 Results: Context

Impact factor: Availability of baseline characteristic information to toolkit users

Healthcare setting: Baseline characteristics information is available via patient medical notes and laboratory results systems in the hospital outpatient setting. In other potential settings of use (e.g. drug treatment centres, specialist GP services) the amount of specific information may vary from site to site. The toolkit in its current design is aiming to effectively assess all patient types for HCV treatment, however, if in certain treatment settings or models of care, treatment assessment is limited to, for example confirmed non-cirrhotic patients then sections of the baseline characteristics data set can be easily removed for convenience of use. Alternatively, in settings where access to patient information is limited, the toolkit could be revised and condensed to identify an agreed set of markers that fit treatment assessment in the context of that particular treatment site.

Impact factor: Adaptability among HCPs

Healthcare professional: Different toolkit users may have varying levels of clinical knowledge which may affect their ability to identify some of the information required in this toolkit section. An education session and Microsoft PowerPoint® presentation were provided with the toolkit to aid users. The toolkit validation study aimed to identify differences in clinical knowledge among differing HCPs and how this affects use of the complex intervention toolkit.

Discussion among the stakeholder research group identified that even with multiple reference sources available (e.g. University of Liverpool Website and app), how you interpret DDI data and its clinical relevance in any patient case depends on your skill base and experience as well as the sources of information used in the assessment (233). The impact of HCP type and level of experience on DDI identification will be discussed in the results of the validation study.

Impact factor: Organisational motivations

Organisation motivations that may impact the adoption of the PTPA novel complex intervention toolkit into HCV patient care in Ireland across all models of care were discussed among the stakeholder research group. The following key motivations were identified as being important at different levels within the organisational structure.

- To increase the number of people being treated for HCV infection
- How the PTPA complex intervention toolkit will be incorporated into current clinic practice?
- Is there the potential to combine the PTPA complex intervention toolkit into electronic patient record systems in the future?
- The PTPA could be a shared document among a patient's relevant healthcare team (GP, ID or Hep consultant, clinical nurse specialist, pharmacy (community and hospital), social worker and key worker and patient)
- The toolkit could help to enhance hospital and community HCP relationships and serve as a model for other healthcare specialities.
- Ease of use
- Staff training
- Time to use versus the current standard process and will this have any impact on staffing and resource levels

Impact factor: Barriers or facilitators to intervention implementations

Potential barriers or facilitators to the implementation of the intervention identified by the stakeholder research group:

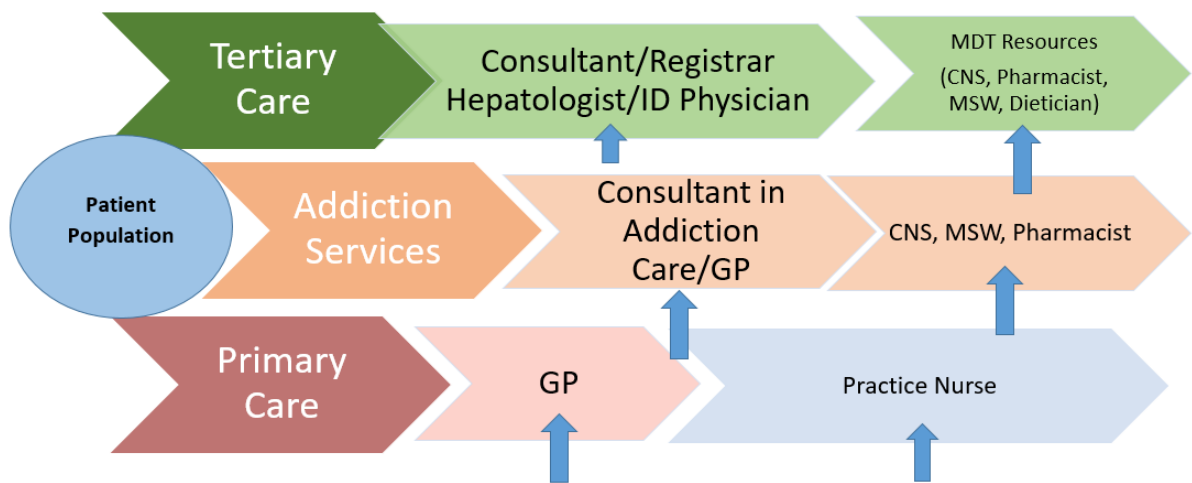
- Time to use. This will be assessed during the evaluation study of the toolkit when it will be compared with current standard of care to identify if it is a more time-consuming process.
- Need to train staff to use the toolkit.
- People already working in the area may not want to change their current practice.
- Access to patient information: The healthcare system in Ireland can be very disjointed across and within different care settings/models of care and therefore the HCP completing the assessment may not have access to, for example, a patient's most recent blood results or most recent ultrasound or oesophago-gastroduodenoscopy (OGD) report.

Impact factor: Context

Contextual factors identified by the stakeholder research group that may impact the outcome of the novel complex intervention toolkit in practice.

- Access to all of a patient's clinical information
- Access to a computer
- A private area to complete a consultation
- Number of members on a HCP team and perceived time to complete these assessments
- Not all information in the toolkit may be relevant to some centres/practices (Community programme only have access to pan-genotypic regimens and do not currently complete their own DDI reviews.
- Not all patients will need all of the bloods listed in the PTPA complex intervention toolkit to assess them for treatment as they may be clearly non-cirrhotic on fibroscan. Also, it may not be possible to get bloods from certain patients (poor access), or a clinic may be running a model of care where there is minimal interaction pre-treatment (e.g. same day turn

around start or 48-hour start). But the toolkit has the potential to be reduced in some settings with feedback from the stakeholder group. The design of the tool at the end of the stakeholder group review was aimed to assess every potential issue with all level of patient up to and including patients with decompensated cirrhosis. From a safety point of view, it is key that all potential risks are searched for, or considered. The toolkit is also an educational aid and the presence of all potential factors for consideration is teaching users about all the different patient and viral factors that can impact treatment outcome.




*Points along the continuum of care when the complex intervention tool may be utilised. 

Figure 3.13 The continuum of care when the complex intervention tool may be utilised

3.7.3. Phase 2 Results: Rationalisation of the toolkit components

Components not included within the pre-treatment pharmacist assessment complex intervention toolkit.

A decision was made early on in this research project by the stakeholder research group not to include any on-treatment related progress monitoring in the toolkit but that a separate section could be developed to assess the impact of pharmacist-led medication counselling, adherence monitoring, side effects management and outcomes.

Medication appropriateness index (MAI):

The lead researcher considered including calculation of the MAI for all medications recorded during the medication reconciliation process during the toolkit development phase however, it was decided during stakeholder research group review that this was too cumbersome and not fitting with the overall aim of the toolkit to achieve optimum DAA regimen selection.

Medication Regimen Complexity Index (MRCI)

Complex medication regimens impact patient safety as they present adherence challenges for patients. Complexity of medication regimens has been found to be an important predictor of a patient's ability to manage their medications (280). The MRCI is a 65-item instrument that can be used to quantify medication regimen complexity at the patient level, capturing all prescribed and over-the-counter medications (280). Medication adherence is key to the successful completion of HCV therapy. Consideration of the inclusion of the MRCI by the stakeholder research group found that MRCI inclusion would add significantly to the length of the PTPA toolkit. The active completion of medication reconciliation and the layout of the medication reconciliation section of the PTPA gives a clear picture of all medications in use by a patient and the source. It was felt that these processes would provide the HCP utilising the toolkit for HCV treatment assessment a clear picture of the complexity of a patient's existing daily medication routine and flag those in need of adherence

support during HCV therapy.

3.8. Complex intervention toolkit Phase 3: Pilot study of the complex intervention

A pilot study should address the main uncertainties that have been identified in the development work. The piloting stages of a complex intervention also include estimating the likely rates of recruitment and retention of participants to any intervention evaluation, and the calculation of appropriate sample sizes for study evaluation. Pilot study results should be interpreted cautiously when making assumptions about the required sample size and response rates when the evaluation is scaled up (258). Effects may be smaller or more variable and response rates lower when the intervention is expanded to a larger scale evaluation.

Substantial development and piloting work are key to ensuring proper consideration of the practical issues of implementation. Completion of optimisation processes provides researchers with important information about the potential effectiveness of their interventions and helps to inform decisions on whether to proceed to the next stage of large-scale intervention evaluation. Given current financial constraints and the pressure to reduce waste and increase value in health services research, pre-evaluation optimisation strategies are key to reduce the likelihood of design or implementation failure and to maximise the intervention's potential for effectiveness (260).

3.9. Phase 3: Pilot study: Method

Study objective

To test the intervention toolkit that has been developed and to identify its potential effect.

Method

A small controlled pilot study was undertaken. Four healthcare professionals were recruited using convenience sampling, to participate in this pilot study. Study participants were divided into two groups of three.

This pilot study did not involve the active care of patients with HCV. For the purposes of this PTPA complex intervention toolkit pilot study, a random sample of two anonymised patient cases were selected from the National HCV patient registry. The same set of randomly selected patient cases will be assessed by both groups. Group A were provided with the draft design PTPA complex intervention toolkit. Group B were asked to completed the same patient cases as Group A but were not be provided with the intervention tool. The PTPA complex intervention toolkit was compared to the current standard of patient assessment prior to initiation of HCV treatment. Current standard of care denotes care or clinical judgement as usual.

Participant recruitment and consent

Participants were invited to participate via email. The participation request email provided a study information leaflet which gave a brief description of the study background and its aims and objectives. Informed consent was obtained by the research team through email replies to pilot study participation emails. The initial study participation invitation email provided selected participants with the opportunity to refuse participation.

Participant randomisation

Assignment of recruited healthcare professionals to the PTPA complex intervention toolkit group versus non-toolkit group: The lead researcher generated the group allocation sequence by using Microsoft Excel® to generate pseudorandom numbers.

Data Collection

Group A (PTPA complex intervention toolkit): Group members were asked to document treatment decisions, rationale and time required on copies of the PTPA complex intervention toolkit provided. (Appendix 15)

Group B (Current standard of care): Group members were provided with a report form to document treatment decisions, rationale and time required for each case reviewed. (Appendix 16)

Data management

- Data collated from participants were entered into a database for further analysis.
- Excel® and SPSS® were used for database development, storage and analysis.
- Data collected as part of this study was irrevocably anonymised on entry into the Microsoft excel database.

Data/Statistical Analysis

Descriptive statistics (percentages and t-tests) were utilised to analyse the variation in results among pilot study participants.

3.10. Results: Phase 3: Complex intervention toolkit pilot

The pilot study was completed by a convenience sample of four healthcare professionals. Two HCPs utilised the toolkit to complete two test cases while two other HCPs completed the test cases using current standard of care. The pilot study permitted further refinement of the complex intervention toolkit and also assessed face and content validity in addition to the feasibility and acceptability of intervention delivery. The pilot study provided preliminary objective data on complex intervention toolkit use. PTPA toolkit use resulted in the correct DAA regimen being chosen in 100% of test cases (4/4) (Table 3.6). Without toolkit use, the correct DAA regimen was chosen in 75% of test cases (3/4). This represents a 25% improvement in optimum HCV treatment regimen selection within the complex intervention toolkit user group as compared with the control (current standard of care) group. Expert statistical advice was sought to utilise the findings from this pilot study to confirm the sample size required for the PTPA evaluation study.

Table 3.6 Pilot Study Test Case Results

HCP	Case 1	Case 2
HCP 1 <i>PTPA complex intervention toolkit in use.</i>	Appropriate HCV regimen and duration selected. No DDIs with regimen selected which was correct.	Optimum treatment and duration selected. Drugs at risk of DDI mentioned but incorrect management plans provided.
Time taken	20 mins	25 mins
HCP 2 Completed without access to <i>complex intervention toolkit.</i>	Appropriate HCV regimen but not duration selected. No DDIs with regimen selected which was correct.	Suboptimal regimen selection and treatment duration. Drugs at risk of DDI mentioned but incorrect management plans provided.
Time taken	20 mins	25 mins
HCP 3 <i>PTPA complex intervention toolkit in use.</i>	Appropriate HCV regimen and duration selected. No DDIs with regimen selected which was correct.	Optimum treatment and duration selected. DDIs identified and management plans given.
Time taken	25 mins	20 mins
HCP 4 Completed without access to <i>complex intervention toolkit.</i>	Appropriate HCV regimen and duration selected. No DDIs with regimen selected which was correct.	Suboptimal regimen selection and treatment duration. No DDI information provided.
Time taken:	15 mins	23 mins

3.11. Main study findings for design and development phase of the complex intervention toolkit

A complex intervention has several dynamic interacting components. Its development is a dynamic process including content review and refinement on a continual basis as the complex intervention toolkit development progresses through initial design to pilot and feasibility testing. The ongoing refinement of the complex intervention toolkit and development using a pre-determined strategy ensures that the interventions are developed systematically, and incorporate evidence based practice (268). The PTPA complex intervention toolkit design and development study created a functional tool guided by the positive evidence base identified for the pharmacist-led activities of medication reconciliation and DDI assessment. The PTPA complex intervention toolkit aims to guide HCPs in the completion of key medication safety processes. Literature review identified a wide range of complex intervention processes in healthcare settings. A key guiding resource identified in complex intervention toolkit development was the UK MRC guidance on the development and evaluation of complex interventions (262, 267). This served as a model during PTPA tool development. Completion of a pilot study highlights the importance of giving consideration to practical issues of use. The positive outcomes of the pilot study along with the strength of the evidence from the primary studies completed, in addition to stakeholder feedback led to the progression of the project to the toolkit evaluation stage. The next phase of the PTPA complex intervention tool development focused on evaluation of the complex intervention toolkit and an assessment of its feasibility and implementability by healthcare providers.

3.12. Complex intervention toolkit Phase 4: Evaluation

3.12.1. Assessing complex intervention effectiveness: Intervention toolkit evaluation study

There are many study designs to choose from, and different designs suit different questions and different circumstances. Awareness and consideration of the range of experimental and non-experimental approaches is important to ensure more appropriate methodological choices. The choice of study design should be made on the basis of specific characteristics of the given study, such as expected effect size and likelihood of bias (Table 3.7) (261).

Table 3.7 Types of evaluation studies for complex interventions

Individually randomised trials	Individuals are randomly allocated to receive either an experimental intervention, or an alternative such as standard treatment, or a placebo (262).
Cluster randomised trials	Study participants are randomly allocated to the experimental or a control intervention (262).
Stepped wedge designs	In this type of trial design, the whole study population receives the intervention, but with randomisation built into the phasing of implementation (262).
Preference trials and randomised consent designs	Practical or ethical obstacles to randomisation can sometimes be overcome by the use of non-standard designs. For example, if the study patient population have very strong opinions about treatments, basing treatment allocation on patients' preferences, or randomising patients before seeking consent, may be appropriate (262).

Randomisation

One should always consider randomisation as a key part of any intervention evaluation, because it is the most robust method of preventing selection bias that occurs whenever those who receive the intervention differ systematically from those who do not, in ways likely to affect outcomes. If a conventional individually-randomised parallel group design is not appropriate, there are a number of other experimental designs that should be considered (262). Post-hoc adjustment is a second-best solution, because it can only deal with known and measured confounders and its efficiency is limited by errors in the measurement of the confounding variables. In some circumstances,

randomisation may be unnecessary and other designs preferable, but the conditions under which non-randomised designs can yield reliable estimates of effect are very limited (262). They are most useful where the effects of the intervention are large or rapidly follow exposure, and where the effects of selection, allocation and other biases are relatively small (262).

Outcome measures

A crucial aspect of the design of an evaluation is the choice of outcome measures. The relative importance of study outcomes must be considered. Primary outcomes will be those which are most important to the study aims. Consideration must be given to how both primary and secondary outcomes you will be dealt with in the study analysis. A single primary outcome, and a small number of secondary outcomes, is the most straightforward from the point of view of statistical analysis. However, this may not represent the best use of the data, and may not provide an adequate assessment of the success or otherwise of an intervention which may have effects across a range of domains (261).

A good theoretical understanding of the intervention, derived from careful development work, is key to choosing suitable outcome measures. You need measures that are appropriate to the design of evaluation. For example, subjective or self-reported outcomes may be unreliable, especially if the study is unblinded. No matter how thorough the development and optimisation work prior to commencement of the evaluation stage, there must be awareness of the possibility of unintended and possibly adverse consequences (261). Finally, you need to consider which sources of variation in outcomes are important, and carry out appropriate subgroup analyses. For example, in the case of public health interventions which are expected to impact on inequalities in health, analyses by socio-economic position may be needed (262).

3.12.2. Complex intervention implementation

Implementation methods must be considered from early stages in the complex intervention development process.

Dissemination of complex intervention design and optimisation

To have a chance of getting findings translated into routine practice or policy, there is a need to make them available using methods that are accessible and convincing to decision-makers. It has long been recognised that passive strategies are ineffective at getting evidence into practice. Information needs to be provided in accessible formats and disseminated actively. Where possible, evaluations should be reported according to established guidelines, as this will help to ensure that the key information is available for replication studies, systematic reviews and guideline development.

A complex intervention, however 'complicated', should strive to be reproducible. Therefore, there must be a full description of the intervention documented and disseminated, and an understanding of its components, so that it can be delivered faithfully during the evaluation, allowing for any planned variation, and so that others can implement it outside your study (Figure 3.14) (262). It is also important to describe the context in which the intervention was developed, applied, and evaluated, so that those reading or attempting to reproduce the intervention can determine the relevance of the results to their own situation (258).

Getting evidence into practice

Strategies to encourage implementation of evaluation findings, if they are found to be effective by RCT, should be based on a scientific understanding of the behaviours that need to change, the relevant decision-making processes, and the barriers and facilitators of change. If the intervention is translated into routine practice, monitoring should be undertaken to detect adverse events or

long-term outcomes that could not be observed directly in the original evaluation, or to assess whether the effects observed in the study are replicated in routine practice (262).

Further research may be needed to assist the process of implementation, and implementation research teams should include a behavioural scientist (262). Lack of impact may also reflect implementation failure rather than genuine ineffectiveness. A thorough process evaluation would be warranted to identify implementation problems in these instances. To enable conclusions to be drawn about complex intervention implementation, a process evaluation will need to be completed.

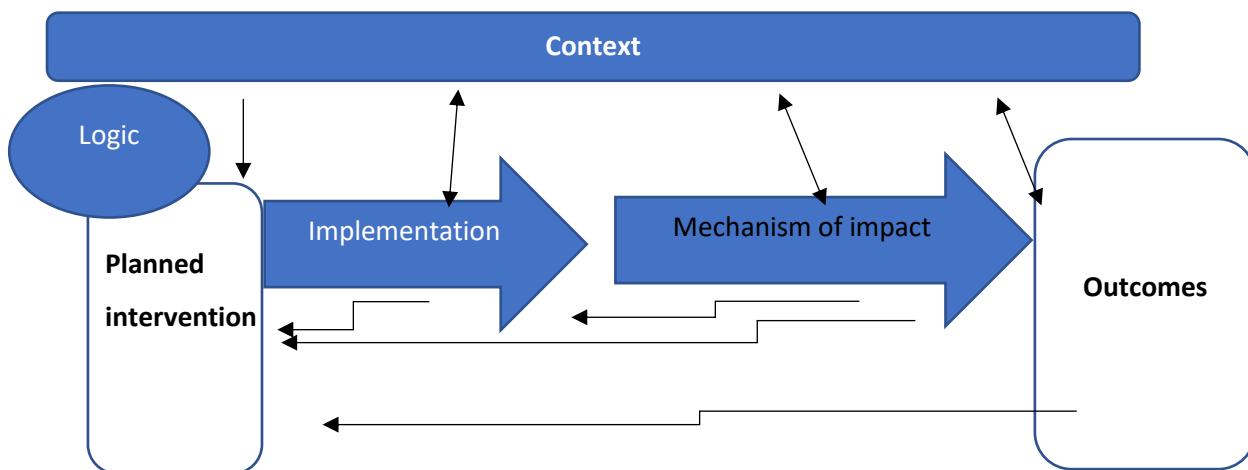


Figure 3.14 Complex intervention development from initial design to outcome analysis

3.13. Complex intervention toolkit Phase 4: Evaluation Method 1: Assessing effectiveness of the complex intervention toolkit

Study aim

This study aimed to provide information on the validity of the pre-treatment pharmacist assessment complex intervention toolkit in helping healthcare professionals chose the optimum HCV treatment regimen selection for specific patients.

Study design

This is a matched cohort study design. A matched group study design was employed to identify if utilisation of the PTPA complex intervention toolkit by healthcare professionals to complete sample patient cases led to a change in the primary outcome of optimum HCV treatment regimen selection.

The matched study design included three arms of HCPs, namely doctors, nurses and pharmacists. This study design was chosen to allow for assessment of the difference in intervention effect between and among differing healthcare professional groups. This study design also helped to assess domain validation which is considered the strongest validation evidence that a prediction rule can be generalised to new patients (281). Domain validation refers to testing the applicability and effectiveness of the complex intervention toolkit across different domains, in this care, different healthcare providers from different backgrounds (281).

Study setting

This study was completed at secondary and tertiary HCV patient care sites in Ireland.

Research Ethics Approval

Ethics approval was obtained from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee. REC Reference 2017-06 Chairman's Action (19). Date approved: 30/06/2017. (Appendix 21).

During the lifetime of this research project, the 2018 Health Research Regulations came into effect. Data collected as part of this research project was collected in 2017 and the first six months of 2018 and participant information collected was fully anonymised. Therefore, this project is in compliance with Health Research Regulations and GDPR.

Study participants

Hospital consultants, non-consultant hospital doctors, clinical nurse specialists and pharmacists.

Eligibility criteria

Inclusion criteria:

Participants must be currently employed as a doctor, nurse or pharmacist and have experience working in the area of HCV patient care.

Exclusion criteria:

- a) HCPs involved in the initial development of the complex intervention toolkit.
- b) HCPs who participated in preliminary pilot analysis of PTPA intervention toolkit use.

Intervention

A PTPA complex intervention toolkit has been designed, developed and optimised. This study aimed to evaluate its effectiveness.

Intervention to be evaluated: The intervention to be assessed for validation was the PTPA complex intervention toolkit (See Appendix 15). The intervention toolkit consisted of five domains which captured patient information which was deemed relevant (during the intervention design process) to selecting the optimum HCV DAA treatment regimen. These domains included, patient baseline characteristics, medication reconciliation, review of the proposed HCV treatment regimen, DDI review and MDT HCV DAA regimen selection outcome and management plans.

Comparator: The PTPA complex intervention toolkit will be compared to the current standard of patient assessment prior to initiation of HCV treatment. Current standard of care denotes care or clinical judgement as usual.

This study did not involve the active care of patients with HCV. Study participants were asked to complete patient test cases with or without the complex intervention toolkit. For the purposes of this PTPA complex intervention toolkit validation study, a random sample of anonymised patient cases were selected from the Irish National HCV treatment registry. The same set of randomly selected patient cases were assessed by all participants regardless of the HCP group or study arm they were randomised to.

Patient characteristics which were identified as important to capture in the test case group included liver cirrhosis (compensated and decompensated), HIV co-infection, previous HCV treatment, patients on opioid substitution therapies, patients with a history of mental health conditions, a gender and ethnicity mix reflective of real-world prevalence, a mixture of genotype, patients with DAA resistance, HIV/HCV co-infection and patients with different HCV acquisition risks. The validation test cases are representative of national burden of HCV infection in terms of gender breakdown, age range, co-infection with HIV, routes of acquisition and disease staging.

Participants randomised to Arm A within each study cohort were provided with the PTPA complex intervention toolkit. Participants randomised to Arm B did not receive the intervention toolkit.

When participants were randomly assigned to specific study arms, they were supplied with a participant pack which consisted of:

- 8 patient test cases (All participants) (Appendix 17)
- Arm A participants received 8 copies of the PTPA complex intervention toolkit
- Arm B participants received a PTPA evaluation study test cases: Case decisions and patient intervention record form (Appendix 16)
- Time to completion record form (All participants) (Appendix 18)
- All participants were supplied with a list of all HCV DAA treatment regimens licensed for use in Ireland and links to the webpages for the EASL and the American Association for the Study of Liver Diseases (AASLD).

Prior to dissemination of the participant packs, the patient test cases were reviewed by the lead researcher and members of the stakeholder research group. The optimum treatment regimen for each case was documented, along with all relevant DDIs and patient interventions in each case. This master document was then used as a basis to assess the responses received from all participants.

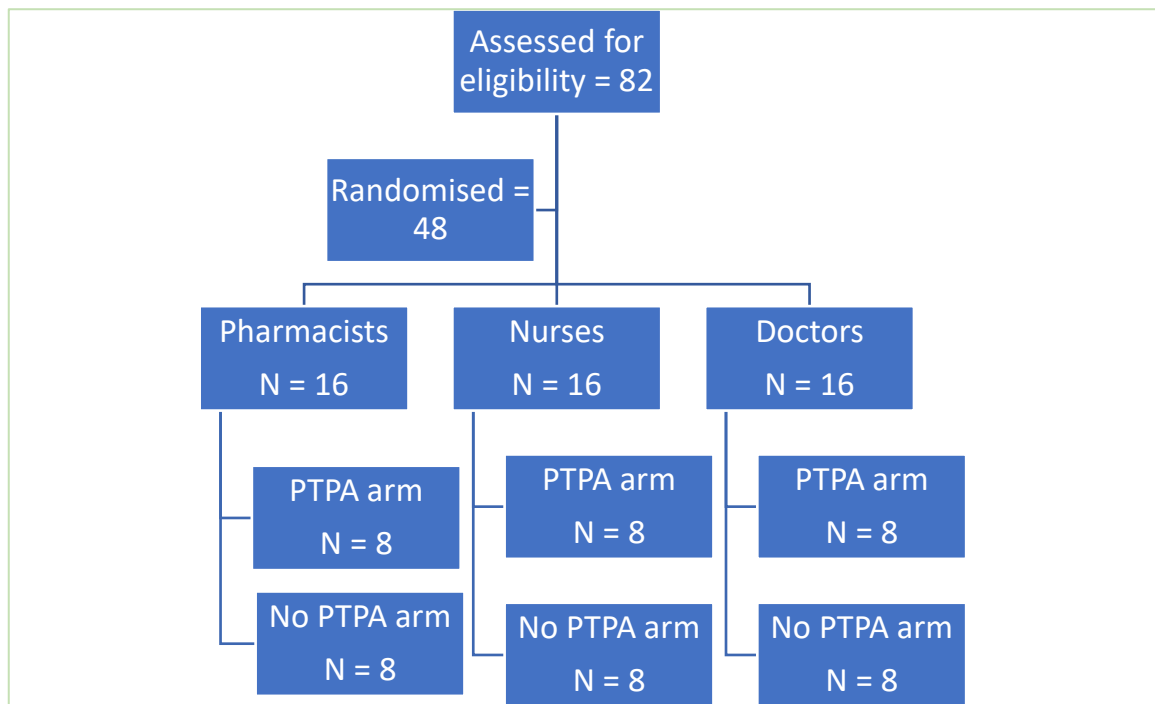


Figure 3.15 Randomisation arms for the evaluation study.

Materials

A training presentation was developed for use by the PTPA complex intervention toolkit arm. The presentation provided an explanation of the 5 domains within the intervention toolkit (Appendix 19). A list of key references for identification of DDIs was collated and circulated to all participants (Appendix 5).

Modifications

No modifications were made to the intervention toolkit during the period of the evaluation study.

Outcomes

The primary endpoint was selection of the optimum treatment regimen for a patient test case.

Secondary endpoints included time to completion, detection of DDIs and patient interventions.

Sample size

A sample size of 58 test cases per study group was calculated. Preliminary pilot testing of the PTPA complex intervention toolkit among the target research participant group indicated that use of the PTPA toolkit resulted in a 25% improvement in the rate of optimum HCV treatment choice as compared with no toolkit use.

Expert statistical advice was sought to confirm the power for this study. It was advised that to compare difference in regimen selection with and without toolkit use in an evaluation study, estimating a 25% improvement in a classical hypothesis test (at a significance level of 0.05) a total of 58 patient cases per arm would be required to achieve 80% power.

There were three cohorts within this matched study design, one specific to each group of HCPs. Therefore, a total of 48 participants (16 participants per cohort) were recruited using a pre-designed study sampling frame. Per cohort, eight healthcare professionals were assigned to each of the two study arms via a concealed randomisation method (Arm A: Complex intervention toolkit use and Arm B: Standard practice). Each HCP within each arm of the study were asked to complete 8 patient test cases.

The study consisted of three groups/cohorts which were stratified by healthcare profession. Each group aimed to recruit 16 participants.

- Group 1: Pharmacists
- Group 2: Clinical nurse specialists
- Group 3: Consultants & registrars

Recruitment

A list of all consultants, registrars, clinical nurse specialists and pharmacists involved in HCV patient care in Ireland was collated. The list of HCPs was stratified by profession in to three groups, nurses, doctors and pharmacists to form three distinct recruitment cohorts. All HCPs collected in the

sampling frame cohorts were assigned a unique number. Random number generation was then used to determine which HCPs would be contacted to request participation in this validation study. The concealed randomisation method ensured that the lead researcher was blinded to which HCPs were selected for recruitment to the study.

Once selected at random, a participation request email was forwarded to the relevant healthcare professionals. The participation request email provided a study information leaflet which gave a brief description of the study background and its aims and objectives (Appendix 20). HCPs were then given a two-week time period to reply to the invitation to participate in the study. If no reply was obtained from the HCP within this timeframe or the HCP declined to participate in the study, the random number generation process was used to select another participant from the relevant HCP sampling frame cohort.

Informed consent was obtained by the research team through email reply to the study participation request email. The initial study participation invitation email provided selected participants with the opportunity to refuse participation.

Randomisation

The study consisted of three groups/cohorts which were stratified by healthcare profession (Figure 3.15). Each group aimed to recruit 16 participants.

- Group 1: Pharmacists
- Group 2: Clinical nurse specialists
- Group 3: Consultants & registrars

Once participants were recruited to each cohort, the next step was to randomise participants to one of the two study arms.

Arm A = Complex intervention toolkit use

Arm B = Standard or care/Current practice

The randomisation process was completed using a concealed randomisation method. The lead researcher generated the study arm allocation sequence by using Microsoft Excel® to generate pseudorandom numbers. This ensured that the lead researcher was blinded to the assignment of participants to the different study arms. The allocation sequence was implemented via an email cascade to recruited participants by the lead researcher.

Blinding

When participants were randomly assigned to specific study arms, they were supplied with a participant pack which was assigned a specific study number, which was linked to the pseudorandom numbers assigned to them by the Microsoft Excel® database utilised during the recruitment and randomisation processes. Participants were asked not to record their names on the study participant pack to ensure that when the researcher was assessing the study outcomes, they remained blinded to the identity of the specific healthcare professional.

Data collection

Data was collected on paper as part of the participant packs which were returned by the study participants either by hard copy or by email. This data was then transferred to Microsoft Excel® and ultimately exported to SPSS® to facilitate statistical analysis. Data collected as part of this study was irrevocably anonymised on entry into the Microsoft Excel® database. The study dataset for the test case results underwent a systematic quality control procedure according to van den Broeck 2005 to ensure the rigour to the results as data entry to the Microsoft Excel® database occurred (247). The quality control procedure involved undertaking a double data entry protocol for a random 10% of the test case results to determine the extent of errors. The cleaned database was then analysed. Development and validation of the study database including quality control checks were completed by the primary investigator and a second nominated member of the research team.

Data analysis

Data analysis was undertaken in St. James's Hospital by the lead researcher using the master document to assess the responses received from all participants.

Statistical analysis

Statistical advice was sought to guide best analysis of the research data in relation to study outcome measures. Descriptive statistics were used to analyse and present characteristics of the study participants and the results of test case completion with and without toolkit use. Statistical analyses of the study findings were performed using IBM SPSS (version 24.0)® with significance levels set at $P \leq 0.05$.

Primary outcome analysis: Selection of the optimum HCV DAA prescription

Statistical analysis was completed to assess variation between groups. The matched design of this study also lends itself to analysis using McNemars test for paired proportions.

Secondary outcome analyses

Time to completion of test cases

Descriptive statistics (mean, median) and t-test analysis were used to assess the difference in time to completion between participants completing the test cases with and without the intervention toolkit.

Rate of detection of drug-drug interactions

Descriptive statistics were utilised to describe the rate of DDI identification within both study arms among all three HCP groups. T-test ($p < 0.05$) analysis permitted assessment of variation between different those completing the test cases with and without the intervention toolkit.

Rate of identification of patient interventions

Descriptive statistics were utilised to describe the rate of identification of patient interventions within both arms among all three HCP groups. T-test analysis permitted assessment of variation between different study arms.

Methods for additional analyses, such as subgroup analyses and adjusted analyses.

The interrater correlation coefficient (ICC) was used to assess any differences within the toolkit intervention user group in each HCP cohort in terms of primary and secondary outcomes.

Data management

Primary access to the evaluation study database was restricted to the lead researcher and co-investigators. Data collected as part of this study was irrevocably anonymised on entry into the Microsoft Excel® database. Data is held on a secure server in St. James' Hospital. St. James' Hospital have strict data protection measures in place. Data confidentiality is ensured at all times. The electronic database will be retained for 5 years on the secure server. After this time has elapsed, the data will be deleted.

3.14. Complex intervention toolkit Phase 4: Evaluation Method 2: Understanding the change process: Survey on complex intervention toolkit use and acceptability among healthcare professionals.

An important piece of evaluation which was completed in tandem with complex intervention toolkit evaluation was analysing the experience of intervention toolkit users who participated in this study.

Study objective

To determine healthcare professional perceptions and opinions on the PTPA complex intervention toolkit use in healthcare and its potential for use in HCV treatment.

Study design & setting

This was a qualitative study which was undertaken post completion of the matched cohort study design to assess the effectiveness of the PTPA complex intervention toolkit. This study was completed at secondary and tertiary HCV patient care sites in Ireland.

Study participants

Hospital consultants, non-consultant hospital doctors, clinical nurse specialists and pharmacists.

Eligibility criteria

Inclusion criteria: Participants must have participated in the matched cohort study design to assess the effectiveness of the PTPA complex intervention toolkit.

Exclusion criteria: Healthcare professionals who had not participated in the matched cohort study design to assess the effectiveness of the PTPA complex intervention toolkit.

Research Ethics Approval

Ethics approval was obtained from the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee. REC Reference 2017-06 Chairman's Action (19). Date approved: 30/06/2017. (Appendix 21).

During the lifetime of this research project, the 2018 Health Research Regulations came into effect. Data collected as part of this research project was collected in 2017 and the first six months of 2018 and participant information collected was fully and irrevocably anonymised at that time. Therefore, this project is in compliance with Health Research Regulations and GDPR.

Method

An electronic questionnaire was developed using the online survey platform, Survey Monkey® (www.surveymonkey.com). Data on participant demographics and their knowledge and perception of complex interventions and their use in healthcare were collected in this short anonymous survey. (Appendix 22) The survey contained 10 questions in total. Questions were divided into three domains, participant demographics, participant opinion on key patient and system factors in optimum HCV treatment outcomes and knowledge of complex intervention use in healthcare and opinions on the potential use of complex interventions in HCV patient care. Questions ranged in type from closed, yes/no questions, ranking questions (0-10), to probing follow-on questions which aimed to elaborate and clarify participant views further. The survey was piloted by three stakeholder representatives from the research group prior to wider dissemination.

Outcome measures:

- Healthcare profession and HCV treatment experience levels among survey participants
- Current barriers in HCV patient care that participants have encountered.
- Current perception of intervention tools in healthcare among healthcare professionals

- Knowledge and use of intervention toolkits already available in the healthcare setting
- The potential role for this complex intervention toolkit in HCV patient care

Recruitment and consent

All validation study participants were invited via email to complete an online survey (link provided) at the end of the test case review period. The participation request email provided a study information leaflet which gave a brief description of the study background and its aims and objectives (Appendix 20). Informed consent was obtained by the research team through email reply to the study participation request email. The initial study participation invitation email provided selected participants with the opportunity to refuse participation.

Sampling

All participants who were randomly selected for, and agreed to, participation in the PTPA evaluation study were included in this study cohort. This included clinical nurse specialists, pharmacists, hospital consultants and registrars.

Sample size

As per sample size calculated for the PTPA evaluation study. (N= 68)

Data collection

Data was collected via the online survey software system, Survey Monkey®. Once the end of the survey study period was reached (five weeks after the end of the validation study period, and four weeks after dissemination of the survey participation request via email) the data collected via the Survey Monkey® online survey software was downloaded for analysis. At this point that data was converted to a Microsoft Excel® database.

Qualitative data analysis

Data analysis was undertaken in St. James's Hospital by the primary investigator.

Analysis software within the Survey Monkey® online survey software permitted completion of some data analysis automatically. This included:

- Key word or word cloud analysis
- Summaries of answers to each question

Data was then downloaded from Survey Monkey® and entered into a Microsoft Excel® database to permit further analysis.

While the online survey data analysis software package, Survey Monkey® completes some baseline data analyse, it cannot replace the role of the researcher in interpreting the qualitative data collected. Data analysis aimed to identify recurrent themes within the collated data. Narrative comments were analysed using a grounded theory approach to identify emerging patterns and themes. Analysis drew on the constant comparison method, operationalised within a general thematic approach. Collated themes and patterns identified were then interpreted in tandem with findings of the literature review, the process map and logic model developed and the stakeholder/research group discussions.

Statistical analysis

Analysis software within the Survey Monkey® online survey software permitted completion of some data analysis automatically. This included:

- Survey response rate (broken down by HCP group)
- Mean time to survey completion
- Summaries of answers to each question using participant numbers and percentages

Data was then downloaded from Survey Monkey® and entered into a Microsoft Excel® database to permit further analysis. Quantitative data were further analysed using descriptive statistics.

Data management

Primary access to the survey results database was restricted to the primary investigators and co-investigators. Data is held on a secure server in St. James's Hospital. St. James's Hospital has strict data protection measures in place. Data held within the database is fully and irrevocably anonymised. Data was downloaded from the Survey Monkey® online survey software system at the end of the study period. At this point the data on the online survey software system was deleted and the survey closed and deleted.

3.15. Results: Phase 4: Complex intervention toolkit evaluation

Assessing complex intervention effectiveness: Intervention toolkit evaluation study

Participant flow

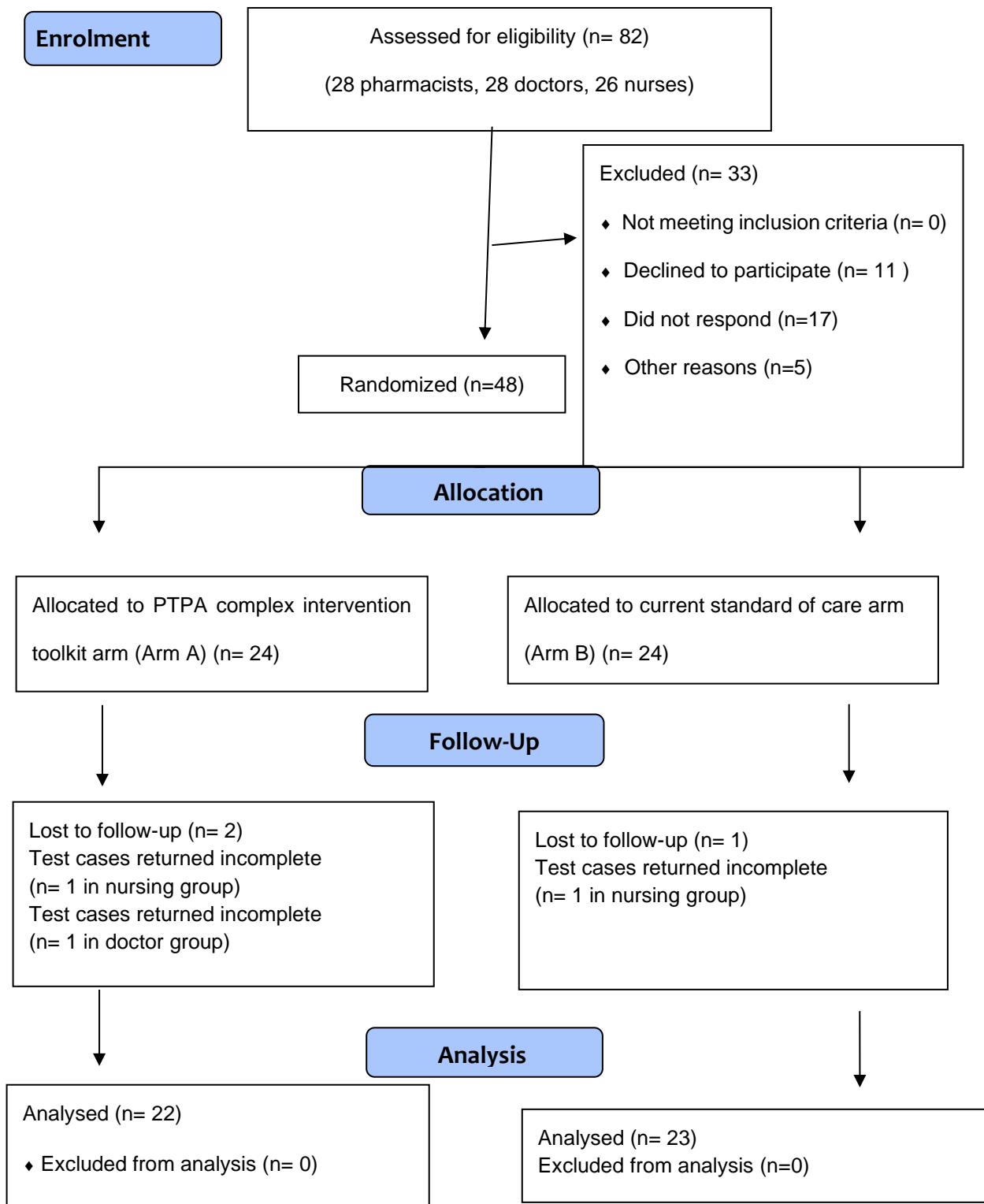


Figure 3.16 Study Participant Flow Diagram

3.15.1. Phase 4 Results: Group 1: Pharmacists

Numbers analysed

A total of 64 test cases were completed by both the PTPA complex intervention toolkit arm (Arm A) and the standard of care arm (Arm B). This represents a 100% completion rate by the pharmacy study participants (Figure 3.16).

Primary outcome measures

- PTPA complex intervention toolkit use was associated with selection of the optimum HCV treatment in 93.8% of cases, compared with 60.9% of cases in arm B (Chi² statistic $p < 0.05$ and McNemars test statistic: $p < 0.05$).
- DDI detection rates increased with complex intervention toolkit use (61% vs 44.9%; T-test 2.974; $p < 0.05$).
- PTPA complex intervention toolkit users proposed an average of 2.6 interventions per test case versus 1.8 interventions per case in Arm B. This difference was found to be statistically significant on t-test analysis. (T-test 3.98; $p < 0.05$).
- The toolkit was associated with a longer median completion time (20 versus 15 minutes), however this difference was not statistically significant ($p = 0.06$).

Sub-analyses

Intra-class correlation coefficients (ICC) were calculated for two of the outcome measures among the PTPA complex intervention toolkit arm (Arm A).

- For DDI detection among the group utilising the toolkit excellent ICC was identified (0.95; 95% confidence interval: 0.88-0.99).
- For patient intervention identification rates among the group utilising the PTPA, there was a low level of ICC (0.649; 95% confidence interval: 0.27,0.9).

3.15.2. Phase 4 Results: Group 2: Clinical nurse specialists

Numbers analysed

A total of 56 test cases were completed by both the PTPA complex intervention toolkit arm (Arm A) and the standard of care arm (Arm B). This represents a 87.5% completion rate by the clinical nurse specialist study participants (Figure 3.16).

Primary outcome measures

- PTPA complex intervention toolkit use was associated with selection of optimum HCV treatment in 76.8% of cases, compared with 57.1% of cases in arm B. However, this difference was not found to be statistically significant (Chi² statistic $p:0.28$; McNemars statistic $p: 0.148$).
- DDI detection rates increased with complex intervention toolkit use (58.2% vs 41.8%). This difference was not found to be statistically significant (T: 1.888; $p 0.061$).
- PTPA complex intervention toolkit users proposed an average of 2 interventions per case versus 0.98 interventions per case in arm B. This difference was not found to be statistically significant (T: 1.18; $p: 0.242$).
- The toolkit was associated with a statistically significantly longer median completion time (19.25 versus 5 minutes). ($p<0.05$)

Sub-analyses

Intra-class correlation coefficients were calculated for two of the outcome measures among the PTPA complex intervention toolkit arm (Arm A).

- For DDI detection among the group utilising the PTPA excellent ICC was identified (ICC 0.94; 95% confidence interval: 0.27-0.9).
- For patient intervention identification rates among the group utilising the PTPA, there was poor intraclass correlation (-0.171; 95% confidence interval: -1.22, 0.67).

3.15.3. Phase 4 Results: Group 3: Consultants & registrars

Numbers analysed

A total of 56 test cases were completed by the PTPA complex intervention toolkit arm (Arm A) and 64 test cases by the standard of care arm (Arm B). This represents a 93.75% completion rate by the physician study participants (Figure 3.16).

Primary outcome measures

- PTPA complex intervention toolkit use was associated with selection of optimum HCV treatment in 82.1% of cases, compared with 68.8% of cases in arm B and this difference was found to be statistically significant. (McNemars test statistic: $p < 0.05$).
- DDI detection rates increased with complex intervention toolkit use (55.2% vs 46.6%). This difference was found to be statistically significant (T: 6.31; $p < 0.05$).
- PTPA complex intervention toolkit users proposed an average of 2.4 interventions per case versus 1.3 interventions per case in Group B. This difference was not found to be statistically significant (T: 1.29; $p: 0.199$).
- The toolkit was associated with a longer median completion time (10.25 versus 7 minutes), however this difference was not statistically significant ($p > 0.05$).

Sub-analyses

Intra-class correlation coefficients (ICC) were calculated for two of the primary outcome measures among the PTPA complex intervention toolkit arm (Arm A).

- For DDI detection among the group utilising the PTPA excellent intra-class correlation was identified (ICC 0.89; 95% confidence interval: 0.72-0.97).
- For intervention identification rates among the group utilising the PTPA, there was poor intraclass correlation (ICC -0.25; 95% confidence interval: -1.25, 0.63).

Double data entry checking for a random 10% of the completed test cases, identified six minor data entry errors.

Limitations of this study design:

- The wide confidence interval in terms of intra-class correlation coefficients for patient intervention identification rates among all HCP cohorts imply that these results should be interpreted with caution. Further analysis looking specifically at patient interventions due to toolkit use is warranted.
- The intervention toolkit was evaluated using test patient cases rather than as part of a randomised controlled trial in practice. Future research using the toolkit aims to complete a randomised control trial.

3.16. Results: Phase 4: Complex intervention toolkit evaluation. Understanding the change process

Among the 82 HCPs who were deemed eligible for enrolment in the study, and who received an email inviting them to participate in this study, a total of 25 completed the survey. This represents a respondent rate of 30.5%. The average time taken to complete the survey was 9 minutes and 51 seconds.

A mix of HCPs were represented in the respondent group including doctors (28%), nurses (32%) and pharmacists (40%). The majority of participants reported working in the hospital setting (88%). All HCP respondents were involved in the care of patients with HCV with a wide range of experience levels (Median 3.5 years; Range: 0.17-2 years). HCPs reported completing a wide range of patient focused activities with the majority of respondents involved in assessing patient suitability for HCV treatment and HCV regimen selection or patient on-treatment monitoring. A significant proportion of HCPs reported involvement in identification of DDIs and medication counselling.



Figure 3.17 Participant definitions and understanding of complex interventions

Patient specific factors which respondents felt were key in terms of optimum HCV treatment outcome included, accurate liver disease staging, management of patient co-morbidities, A patient's ability to comply with treatment and completion of the fully prescribed DAA course. Healthcare service factors which respondents felt were key in terms of optimum HCV treatment outcome included, regular clinician and nurse review during the treatment process, adverse effect management, medication counselling and adherence monitoring.

When asked to consider the potential benefit of a complex intervention toolkit to guide optimum HCV direct acting antiviral prescribing, HCPs responded positively with 92% reporting this as a useful potential development in HCV care. When asked to comment more specifically on their answers, respondents stated that a complex intervention toolkit could aid complex treatment decisions and staff training and ensure standardised practice (Figure 4.16). Others reported that a complex intervention toolkit may help staff to evaluate and reflect on current practices.

A high proportion of HCPs reported use of complex intervention toolkits in their current everyday practice (84%). HCPs reported varying definitions and understandings of the term complex intervention toolkit (Figure 3.17). Overall opinions around complex intervention toolkit use in practice were positive. They were seen as useful in decision making, collating multiple patient factors, providing a checklist function and standardising practice. Among those currently using complex intervention toolkits in their everyday practice, feedback was in the main positive. One respondent noted that while complex intervention toolkits are useful, they may have the potential to de-skill staff in certain roles.

Main study findings

The findings of this evaluation study confirm the effectiveness of the PTPA toolkit in aiding pharmacists and doctors in selecting the optimum HCV treatment for patients. The potential for

HCPs working in all practice environments, including community, to safely assess and manage HCV treatment outside of specialist centres, can be supported using this toolkit. This type of capacity building within our limited healthcare resources is key to up-scaling the model of care in Ireland and internationally to achieve World Health Organisation elimination targets.

Key Findings

What was known prior to this study?

- Complex intervention tools facilitate healthcare professionals in making clinical decisions with prior research highlighting their positive impact on consistent patient care and positive patient outcomes.
- No previously published studies have described the design and development of a complex intervention to promote optimum HCV treatment.

What is the added value of this study?

- The research process guided by the MRC framework created a function toolkit guided by the positive evidence base identified in this body of research.
- The findings of this evaluation study confirm the effectiveness of the PTPA toolkit in aiding pharmacists and doctors in selecting the optimum HCV treatment for patients.

Implications of the new findings?

- This research provides a novel approach to expanding the model of care, in the field of HCV treatment.
- This represents an important contribution to the limited data surrounding complex intervention development for use in the area of HCV patient care.

3.17. Strengths of the PTPA complex intervention toolkit design, development and evaluation:

- One strength of this research was the use of HCPs from multiple HCV treatment centres nationally to participate in all steps of this intervention development from participation in the stakeholder research group and feasibility studies to recruitment into the evaluation study. This helped to increase the generalisability of the evaluation study results.
- Another strength of this research was the excellent retention rate of participants in all study groups within the evaluation study.
- Adherence to the UK MRC guidelines for complex intervention design and development.
- The use of primary research to justify inclusion of specific domains within the PTPA complex intervention toolkit (e.g. medication reconciliation and DDI assessment and management).

3.18. Limitations of the PTPA complex intervention toolkit design, development and evaluation:

- Due to the nature of the intervention, it was not possible to blind participants to their allocation within the evaluation study which may have had the potential to introduce the Hawthorne effect. However, this effect is likely to have been present in both the intervention and control arm of the evaluation study.

Chapter 4: Discussion

Phase one of this research specifically highlighted the importance and impact of the processes of pharmacist-led medication reconciliation and DDI assessment and management in ensuring optimum HCV treatment outcomes. The findings of these research studies provided justification for inclusion of these pharmaceutical care activities as building blocks for complex intervention toolkit development.

There has been a steady pace of change within the pharmacotherapy options for HCV infection in the last seven years. With SVR rates surpassing 90% in the general treatment population and the presence of minimal adverse effects confirmed, treatment programmes are expanding internationally to facilitate up-scaling of treatment rates to tackle HCV population prevalence and to achieve WHO elimination targets (69, 282, 283). With this upturn in treatment rates, comes an increase in the heterogeneity of the treatment population, the co-morbidities they present and their co-medication lists. As outlined in the findings presented as part of this research project, pharmacists undertaken multiple patient interventions along the HCV patient care pathway which have demonstrated a positive impact on patient treatment outcomes and patient safety.

4.1. Pharmacist-led medication reconciliation in HCV patient care

Medication reconciliation is defined as ‘the process of obtaining a complete and accurate list of each patient's current medications from all available sources at all points of contact and verifying and reconciling medications to reduce medication errors (198). Medication reconciliation is complex and this is further compounded by the disconnected nature of the Irish healthcare system. The need for data on medication reconciliation and optimal medication management in the outpatient setting is well recognised (44). The Health Service Executive Madden report endorsed the prioritisation of medication reconciliation based on the findings of international and local research which has highlighted the significant medication related error rates in healthcare organisations worldwide

(198, 200). Medication errors are one of the most common types of medical errors and are the most frequent cause of adverse drug events (ADEs) encountered in healthcare resulting in significantly increased morbidity, additional healthcare resource utilisation and increased mortality (4-6). However, to date little if any research has considered the importance of medication reconciliation in the outpatient setting.

The large and diverse range of co-morbidities and co-prescribed medications identified in this study cohort at baseline highlights the heterogeneous nature of real-world populations. Approximately 90% of patients starting DAA therapy were found to be taking at least one co-medication at baseline. A high prevalence of prescribing of methadone (28.7%) and benzodiazepine derivatives (21.7%) reflects the significant proportion of patients with a history of IDU (51.6% of population) within the patient population. Other common co-morbidities including cardiovascular disease, HIV co-infection, depression, gastrointestinal conditions, cirrhosis and chronic pain are reflected in the most commonly prescribed medication classes. A significant proportion of this study population also had a documented history of depression at baseline (28%). This is higher than previously reported in other EU studies (211). The associated prescriptions for anti-depressants and benzodiazepine-related medications are at risk of potential DDIs, particularly with protease inhibitor-containing DAA regimens.

Medication reconciliation identified medication variances affecting 74% of the study population. The only other study which has investigated medication reconciliation in HCV treatment patients reported a higher percentage of patients impacted by medication reconciliation variances (81%), however this study consisted of a much smaller patient group (N = 57) (206). The inclusion of 300 patients within this study cohort provides more robust evidence on the high rates of medication reconciliation variances in the HCV patient population which may pose a risk to patient safety and HCV treatment efficacy. The number of patients impacted by medication reconciliation variances

in this study (74%) is similar or higher to rates reported as part of hospital inpatient medication reconciliation studies which have been conducted (200, 284, 285).

No other study has described the type of medication variances identified in HCV patients at the point of outpatient medication reconciliation. The most frequent type of variance identified was medication omission from the patient medication list (87%). This is a higher rate of errors of omission than described in inpatient medication reconciliation studies (286, 287). A study of pharmacist medication reconciliation completed in the Irish hospital inpatient setting identified that 65.3% of variances identified were errors of omission with dose frequency variances accounting for 22.5% of total variances (200).

In terms of severity of medication variances identified, Chi *et al* reported that only 2% of discrepancies from their medication reconciliation study among HCV patients were classified as significant (206). Using a cut off of greater than or equal to 7 on the VAS rating as severe and significant, our study identified a much higher rate of potentially significant or severe medication reconciliation variances (16.3%). Medications used in the treatment of epilepsy accounted for four high risk variances identified. This is due to the potential for some AEDs (e.g. carbamazepine) to cause induction of drug metabolism pathways (e.g. CYP 450 & P-gp) resulting in a reduction in DAA drug concentrations which may cause HCV treatment failure with the emergence of DAA resistance if not identified and appropriately managed. Conversely, some DAAs may cause an increase in antidepressant and hypnotic medication concentrations due to inhibition of metabolism pathways (e.g. CYP450 3A4). These DDI issues can only be managed appropriately if these medications are first identified as part of the medication reconciliation process.

The findings of this study highlight the importance of completing this key process of pharmacist-led medication reconciliation to ensure an accurate list of co-medications is obtained prior to DDI review. Medication reconciliation has the added benefits of enhancing communication among all

providers of care and engaging patients, HCPs, families and carers more consistently in-patient care. This is the first study to our knowledge that reports the rate, type and potentially severity of medication variances identified during pharmacist-led medication reconciliation in a HCV outpatient clinic.

No other study to date has identified the importance of medication reconciliation as part of the HCV pre-treatment patient assessment. This is the first study to our knowledge which describes this specialist clinical pharmacist role of medication reconciliation among a cohort of HCV treatment patients (210, 213-215, 288). Given the significant rate of medication reconciliation variances identified in this large study cohort and the potential knock-on effect of these variances on HCV treatment outcome and patient safety, it is imperative that medication reconciliation is considered an essential component of HCV patient pre-treatment assessment. The findings of the study led to the rationale for medication reconciliation to become a key component of the complex intervention toolkit developed. It represents a key part of the HCV PTPA as an accurate DDI review cannot be undertaken in the absence of an accurate list of all medications in use by an individual patient. This makes medication reconciliation a key component for inclusion within the design of the complex intervention toolkit.

Given that the care of HCV patients takes place for the most part in the outpatient ambulatory setting, there is a need for on-ongoing and continual review and updating of a patient's active co-medication list during HCV treatment. As outpatients, patients on HCV DAA therapy have access to multiple sources of medications including prescription medicines, OTC products, illicit drug use or CAM products. Patients may interact with multiple HCPs and therefore obtaining an accurate and up to date picture of patient co-medication use relies on patient disclosure but more importantly a detailed patient assessment process which considers all potential sources, formulations and types of potential co-medications.

The findings of this study highlighted the need for standardisation of the medication reconciliation process as part of the HCV patient assessment model of care and indeed among all outpatient managed healthcare specialities. It also makes it an essential component for inclusion in the pre-treatment assessment complex intervention toolkit.

4.2. Drug-drug interactions

It is clear that a significant number of patients are at risk for DDIs when treated with HCV DAAs. To date the only published datasets from real-world cohorts are two studies from the US and Germany reporting the pharmacist-led intervention of DDI assessment (213, 214, 220). Only one of these studies discusses the active management and outcomes of DDIs identified (213). However, this study population consisted mainly of African American males (63.3%) and almost exclusively of patients with genotype 1 infection, which limits its extrapolation to other healthcare populations. In addition, these studies do not report the process of medication reconciliation, the importance and significance of which has been highlighted as part of this research project. Availability of further data on medication reconciliation and DDI occurrence and active management strategies within real world cohorts will enable HCPs to make better informed decisions regarding DAA DDI management.

As described in results from work completed in this project to date, patients with multiple co-morbidities and co-medications are now the norm rather than the exception. Approximately 90% of patients starting DAA therapy were found to be taking at least one co-medication at baseline and 71% of the total study population were at risk of a potential DDI with their proposed DAA treatment regimen, as compared with 80.3% in a recent US study (213). Sicras *et al* examined data on co-morbidities and co-medications in the Spanish HCV patient cohort and determined that 61.6% of co-medications had the potential for DDI should HCV treatment be initiated (288). A high baseline

prevalence of multi-morbidity appears to be driving this polypharmacy and the subsequent risk of DDIs. International guidelines now recommend a minimum of dual DAA therapy for all genotypes (13, 61). On analysis of the top twenty medication classes prescribed in this study cohort, all with the exception of methadone, pose some potential for DDI with multi-DAA regimens.

The average number of DDIs per patient in this study was 1.59. This is less than the DDI rate described by Ottman *et al* (1.85 DDIs per patient) (213). The difference in DDI rate between these two real-world cohorts may in part be due to the older age of the VA cohort (Mean 61 years; Range 26-76 years versus 50 years; Range 25-81) (213). However, when compared with a study by Vermehren *et al*, our findings report a higher DDI rate per patient, even with a lower average patient age (214). Another factor which may have led to an increased DDI rate in the VA study is the disproportionately high rate of genotype 1 patients in the cohort (94.3%), which in turn may have impacted on the choice of DAA regimen and the potential for DDIs. Our study cohort is more consistent with the genotype mix among the wider HCV patient population. However, our study results still highlight a significant DDI rate among the patient population as a whole (289).

A high rate of PPI prescribing in this Irish cohort and their potential for DDI with DAA therapies mirrors findings internationally and highlights again the pattern of overprescribing of PPIs (211, 213, 290). Widespread availability of PPIs in the Irish setting, including OTC sales in community pharmacy is increasing their inappropriate use (211). This high level of PPI prescribing greatly increases the DDI potential of the ledipasvir, velpatasvir and glecaprevir containing regimens. As these DAAs are widely prescribed, this particular DDI issue will continue to hinder treatment efficacy into the future, if not appropriately assessed and managed (291).

An important point to consider is that the DAA may not always be impacted in potential DDIs. DAA DDIs also have the potential to negatively impact management of co-morbidities which may

therefore impact patient safety. Patients with cardiovascular disease are an example of one such group identified in this study. All DAA regimens were found to have the potential to interact with statins and dihydropyridine derivatives. Anti-hypertensives, including dihydropyridine derivatives (e.g. amlodipine) accounted for 10% of dose adjustments made, which is higher than the rate of DDI reported with this medication grouping by Langness *et al* (7%) (215). Vermehren *et al* also highlighted the risk of DDI associated with cardiovascular disease medications however, this was not described in the VA patient study (213-215). In another example from this study, co-prescription of oxybutynin with P/rOD had the potential to increase oxybutynin adverse effects due to the inhibition of the CYP450 3A4 isoenzyme by ritonavir. Oxybutynin dose reduction was required in the case of two patients in this study.

This study cohort included seventy patients with HIV co-infection. Previous studies in this area describe the inclusion of minimal numbers of co-infected patients (213-215). In addition, in the era of IFN, patients co-infected with HIV often achieved lower than anticipated SVR rates (292, 293). The potent efficacy of DAAs finally offer co-infected patients an equal opportunity for SVR attainment. An important consideration in the treatment of HIV patients with DAAs, is assessment for potential DDIs with antiretroviral therapy (210, 294). A previous retrospective chart review study identified that 75% of co-infected patients would require antiretroviral therapy interchange prior to HCV DAA treatment due to DDIs (227, 295). The findings from this cohort confirm this, with antiretroviral therapy alterations required in 49% of patients prior to DAA treatment (289). A further 33% of this patient group required increased monitoring during HCV therapy. It should be noted that the decision to make an antiretroviral regimen switch must be undertaken with careful consideration and planning to ensure HIV therapy is not compromised (295). Extensive antiretroviral histories and resistance along with drug intolerance or heavy pill burden can present barriers to antiretroviral therapy switching and successful HCV treatment initiation in the co-infection cohort (295). Clinical pharmacists play a critical role in this process, as part of the MDT,

to ensure the effectiveness of HIV therapy is not compromised (295). This study represents the largest real-world DDI analysis of antiretrovirals and DAAs to date. The significant number of potential DDIs between DAAs and antiretrovirals causes HIV/HCV co-infection patients to remain a special population from a DDI perspective.

The findings of this study have highlighted that 9% of the study population were prescribed a herbal supplement which had the potential to interact with DAA therapy. Given that 8% of all severe DDI risks identified in this study were linked to these products, it is imperative that their use is identified as part of the pre-treatment pharmacist assessment and assessed, to negate any potential impact on DAA treatment efficacy. This is a key benefit of pharmacist-led medication reconciliation, which helps to identify all patient medications as patients will not always disclose use of supplements, herbal products and multivitamins, as was identified in the CAM survey patient cohort. In addition, if patients procure these products online, it is not always possible to definitively confirm the name and quantity of active constituents. Even if the active constituents of these products are confirmed, information on their pharmacokinetic properties and their potential to interact with medicines is often limited or non-existent. For patients being assessed for DAA therapy it is imperative that use of these products is identified and assessed.

High levels of use of multivitamin (16%) and mineral supplements (10%) was also identified in this study. Multivitamin products almost universally contain compounds that have an antacid effect (e.g. calcium carbonate or magnesium oxide). The constituents therefore have the potential to alter gastric pH on administration. For patients prescribed the regimen of SOF/LDV, this presents a risk to ledipasvir absorption and treatment efficacy. Medicines which have an antacid effect are also cautioned with velpatasvir due to a similar negative impact on DAA absorption. PTPA review in this study facilitated identification of these supplements and development of management plans (e.g. separation of dosing times), to negate any potential impact on DAA treatment efficacy.

Across all potential DDIs identified in this study, the majority (59.5%) were found to be clinically significant, and were rated moderate (45.5%) or severe (14.3%) respectively (289). This represents a higher overall incidence of potentially severe DDIs, as compared with previous studies (210, 211, 220). Protease inhibitors in particular were found to be associated with an increased risk of DDI occurrence, with 13.6% of DDIs identified with the P/rOD regimen, being classified as severe. The DAAs associated with the lowest potential to be involved in a severe DDI were SOF and DCV. Co-medications most frequently associated with severe DDIs included statins, inhaled glucocorticoids and antiretroviral therapy. One example was that of inhaled fluticasone and the DAA regimen, P/rOD. The ritonavir component of this regimen has the potential to cause a significant increase in fluticasone exposure due to inhibition of CYP3A4 isoenzymes which may cause Cushing's syndrome. Effective management of DAA DDIs identified is not widely described in real-world cohorts to date. Ottman *et al* report DDI management among the VA cohort, with 59% of DDIs identified managed through implementation of an increased monitoring plan (213). This is a significantly greater proportion of DDIs managed in this way as compared with this study's cohort (289). Actionable management interventions were much more prevalent in this study (66.5% vs. 41%).

This study reports a five-fold increase in the number of medications discontinued during DAA therapy as compared with the VA cohort. This may in part be driven by the inclusion of CAM products in the DDI review process. However, as highlighted by their potential to be involved in clinically relevant, severe DDIs, this inclusion is warranted. Another factor which may explain the higher rate of medication cessation relates to the significant number of inappropriate PPI prescriptions identified during the medication reconciliation process. Completion of medication reconciliation alongside DDI review permitted identification of these prescriptions which were then reviewed by the clinician to clarify clinical need. The combined impact of these two pharmacist-led interventions is evident from study examples like this and strengthened the justification for inclusion of these elements in the design of the complex intervention toolkit.

This study's findings show a three-fold increase in medication changes due to DDI identification as compared with the study by Ottman *et al* (20.3% vs 6.9%) (213). Potential factors that may be at play here include the inclusion of more HIV co-infected patients. A high proportion of this patient group within the study cohort required antiretroviral changes prior to HCV treatment. There was also a high rate of co-medication relating to cardiovascular disease management and hypnotics and sedatives.

This study has also identified that in some cases co-medications will determine the choice of DAA regimen, a factor which has not been previously described in published research in this area (i.e. refractory epilepsy) (236, 289). For example, co-administration of oxcarbazepine is contra-indicated with all available DAA regimens due to induction of drug transporter P-gp and CYP3A4 isoenzymes, which may lead to a loss of efficacy of the DAA regimen. Therefore, for HCV treatment to proceed, the patient's epilepsy regimen was changed (236). A change in planned HCV DAA regimen was required for eight patients due to severe unavoidable DDIs with anti-epileptic medications and antiretroviral therapy. (236). These differences in DDI management strategies between studies may also reflect the different healthcare settings (US and Ireland).

In addition, there is always a potential for an unexpected DDI (e.g. amiodarone with sofosbuvir) (296). Healthcare practitioners including pharmacists and physicians must be vigilant for potential DDIs in their heterogenous patient populations. The importance of gaining real-world data on DDI occurrence with HCV DAAs is further reinforced when case reports are published highlighting ADEs due to DDIs, which were not identified during patient pre-treatment assessments. For example, a case report published in Australia in 2016 reported a case of Cushing's disease due to an interaction between ritonavir for HCV treatment and oral budesonide for autoimmune hepatitis (297).

As the model of care for HCV treatment evolves, it must ensure that regardless of the treatment setting, patients can engage with a healthcare provider with treatment knowledge and adequate resources, in order to be evaluated and initiated on an optimum and safe treatment DAA regimen (109). The pharmacist is uniquely trained to be able to impact medication safety at the individual patient level in HCV treatment services, through the medication management skills of medication reconciliation and DDI review. A unique feature of this study is that all DDIs reported were identified, investigated, rated for severity and had management plans created by an onsite clinical pharmacist. The majority of management plans (96.9%) proposed were accepted by the prescribing team with 100% of plans proposed for potentially severe DDIs accepted. This is a higher rate of acceptance than that reported by Ottman *et al* and it highlights the success of this HCV pre-treatment pharmacist assessment process (213). This work has demonstrated the importance of the role of the pharmacist as part of the HCV MDT and the recognition of the pharmacist role in identifying and managing DDIs identified to ensure safe and effective HCV therapy.

With multiple DAA regimens now licensed, medication reconciliation and DDI assessment are key, in ensuring that all patients achieve their potential SVR outcomes without hindrance due to unidentified DDIs which may lead to HCV treatment failure, resistance emergence and inadequate management of patient co-morbidities. (216). The findings of these studies build on the real-world DDI evidence available in the setting of DAA therapy to aid clinicians in decision making and ensure optimum SVR outcomes are achieved. Pharmacists are an integral component of the HCV team leading on DAA treatment options, DDIs, patient education, medication supply and adverse effects management (213, 214, 220). Following the licensing of co-formulated SOF/VEL/VOX in 2017, there are now no new DAA regimens on the horizon.

Therefore, the role of the pharmacist as outlined in this study will be key to ensuring HCV antiviral stewardship in the coming years as countries strive to achieve HCV elimination. This description

and assessment of the pre-treatment pharmacist assessment processes of medication reconciliation and DDI assessment and management in the HCV treatment setting may also serve as a model for other HCV treatment services or healthcare specialities of the value gained in terms of patient safety outcomes.

Knowledge of the prevalence and impact of potential DDIs with HCV DAAs in real world cohorts is essential if treatment is to be safely up-scaled to a wider model of care. This study's findings re-enforce the critical importance of the pharmacist-led activities of medication reconciliation and DDI assessment. Management of drug–drug interactions is a critical aspect of clinical practice when using DAAs. As previously stated, the positive findings of both the medication reconciliation and DDI studies provides justification for their inclusion as the building blocks of the HCV pre-treatment assessment complex intervention toolkit.

4.3. Use of complementary and alternative medicines among patients with HCV infection

An emerging trend identified within the findings of the medication reconciliation portion of this research project was the growing prevalence of CAM use within the seropositive HCV population. The high prevalence of CAM use identified led to the expansion of this component of the research project to include a quantitative survey to identify, quantify, describe and categorise use of CAM medicines, multivitamins and supplements among HCV patients.

The findings of the patient survey report a high usage rate among the study population of 44%. This patient survey was completed by a convenience sample of 50 patients. In addition to the limited number of patients in the survey group, the convenience sampling method may have led to more patients with an interest in CAM or using CAM products consenting to participate, which may have biased the results. This rate of almost 50% is similar to previous studies assessing CAM use in the chronic HCV patient population. A US DAA DDI study by Langness *et al* identified a higher rate of

use of vitamin and herbal supplements among their study population (42.7%) (215). Studies by both White *et al* in Canada and Coughlan *et al* in Ireland reported CAM usage rates of 46% and 50% respectively (240, 241). However, it should be noted that the study by Coughlan *et al*, was completed exclusively among patients who were iatrogenically infected with HCV infection (241). The rate of use of CAM products described among the wider medication reconciliation and DDI study cohort is likely to be more truly reflective of the prevalence of use among HCV positive patients in Ireland today.

Previous research has highlighted that the reported prevalence of CAM use in the general population can vary greatly (10—67%) across different countries with increased use reported among patients with chronic healthcare conditions (298). However, this does detract from the fact that regardless of the proportion of patients using CAM, it is important that patients undergo the process of medication reconciliation as part of their HCV pre-treatment assessment so that usage of these products is identified, assessed for the potential for DDI with HCV DAAs and other co-medicines and also assessed in terms of safety of use. CAM products accounted for 10.2% of DDIs identified during the medication reconciliation and DDI study. Therefore, it is key that their use is identified as part of any HCV patient pre-treatment assessment to ensure the DDI risk can be evaluated and managed effectively.

It is noteworthy, that all other survey studies assessing CAM use in HCV positive patients were conducted prior to the availability of IFN-free DAA regimens and their associated high rates of SVR (238-241). In some of these previous studies rates of use of CAM may have been influenced by patients seeking an alternative treatment for HCV and for symptoms they associated with the viral infection. Our study highlights that patients are now using CAM products for a variety of reasons but in the main, the focus of use surrounds improving general health and energy levels. Helping to improve exercise tolerance was also commonly reported as a rationale for use. Two patients

reported use of CAM products to specifically manage liver health. It is possible that dissatisfaction with conventional health care and the perceived failure of medicine to manage chronic disease is another reason that patients may adopt CAM use however this was only reported by one survey respondent in this study. The reasons for use indicate that CAM use may occur across all HCV patient groups and therefore all patients should be questioned about CAM as part of their pre-treatment assessment.

The most commonly used CAM products identified in this study were gym supplements, herbal teas and milk thistle. Across all other studies identified, milk thistle was also among the most frequently reported products in use (238, 240, 241). This is most likely due to previous research published which reported that milk thistle may have the potential to exert beneficial effects in chronic liver diseases through antifibrotic properties (299).

Vitamin use is also consistently high across previous studies, with White *et al* reporting vitamin use among 81% of the study population and 56% reported use in the study conducted by Richmond *et al* (238, 240). However, the rate of vitamin use reported in this study is lower while the use of herbal supplements is greater than in previous published studies at 59%. This highlights the emerging and growing trend of gym supplement usage among HCV positive patients. One other study makes reference to use of diet-based therapies in their patient cohort, however this was a much lower reported rate of use at only 7%. The lack of data on gym supplement use may be due to the exclusion of such products in previous studies. However, given the high rate of use identified within this study and the wide range of products now available for purchase in health food shops, online and in sports clubs and gyms, these products warrant further investigation in terms of potential for DDI or adverse effects.

CAM usage in this study was found to be linked to younger age and to third level education. Similar associations were identified in a study by Ferrucci *et al* in the US which examined used of CAM in patients with chronic liver disease secondary to any cause (239). Two other US-based studies conducted specifically in a HCV patient population also found higher levels of education was statistically significantly associated with CAM usage (237, 238).

A significant proportion of patients reported that they had received information about CAM products from family and friends and various media sources. This mirrors the results of a study by Richmond *et al*(238). This lack of expert consultation raises concerns about the potential for DDIs between CAM products and DAAs or adverse drug effects which are not being assessed by any healthcare professional. Two patients reported receiving information directly from a CAM practitioner and three patients from a healthcare professional. Patients are purchasing products on-line, in health food stores, supermarkets and from CAM practitioners. These products present numerous potential hazards for patients receiving DAA therapy and patients with hepatic fibrosis. The fact that some patients may receive advice about and purchase CAM products without any HCP interaction heightens the risk of potential negative health effects.

Even among patients purchasing CAM products in pharmacies or from providers where they are asked about their co-medications and co-morbidities, only 58% reported that they always disclosed this information to CAM practitioners or when purchasing CAM products from health food shops. This figure drops even further when patients are interacting with HCPs, with only 27% of CAM users surveyed reporting that they always disclose CAM use to HCPs. This may be due to a lack of knowledge about the potential negative effects of non-disclosure but it may also reflect a real or perceived lack of knowledge among HCPs and CAM practitioners about the importance of checking for all potential types of patient co-medications and co-morbidities.

Despite increasing patient usage of CAM, the majority of HCPs are not trained or knowledgeable in this area. This study's findings highlight the need for enhanced patient and practitioner education and communication regarding CAM use. The pharmacist can play a key role in educating both patients and healthcare providers. It is key that CAM use is enquired about by clinicians and others HCPs caring for patients with chronic conditions to ensure their use is not missed from the patient records and overall healthcare picture.

In addition to educating HCPs about the importance of asking patients about their use of CAM products, it is also important that they are aware the risks these products pose in terms of DDIs with co-medications. Multiple products identified during this survey study had the potential to interact with HCV DAAs and therefore patients were requested to discontinue these while receiving HCV therapy. In the DAA DDI study completed as part of this research project, CAM products accounted for 10.1% (N = 48) of potential DDI episodes. These findings re-enforce the importance of checking for use of CAM with every patient being assessed for HCV therapy.

Use of CAM by patients with HCV infection appears to be higher than in the general population. Obtaining an accurate medication list including any CAM products in use is critical to ensure patient safety, identify any DDI risks with DAAs to ensure optimum HCV treatment outcomes and to provide patients and their healthcare providers with information on relevant CAM products in use. The findings of this study highlighted to importance of including specific reference to use of CAM products in the medication reconciliation section of the complex intervention toolkit to ensure users remembered to question patients about potential CAM use. In terms of assessing the potential for interaction between CAM products and DAAs, while the list of CAM products on the University of Liverpool website has grown in recent years, with 32 items now listed, there is still little readily available data on many products. This re-enforced the importance of the development of DDI resource and reference list for use in conjunction with the intervention toolkit.

4.4. Epilepsy medications and HCV co-infection

The broader DDI study identified patients with epilepsy as a subset of patients who require particular focus around DDI identification and management. A sub-study was designed to assess how DDIs between AEDs and DAAs were managed in this patient cohort, and the impact such DDIs had on HCV treatment outcomes and their timeline to HCV treatment initiation.

The availability of multiple HCV DAA regimens now offers all patients with chronic HCV infection the opportunity for treatment, with SVR rates surpassing 90%. Patients with epilepsy are no different, once DDIs are taken into account, as is evident in the SVR rate obtained by patients in this study cohort whom have completed HCV therapy. Excluding the diagnosis of epilepsy, the characteristics of this study group mirrors those of the wider Irish HCV treatment population as identified in previous research (300).

In all patients with chronic HCV infection, management of DDIs is a critical aspect of clinical practice and patient safety when using DAAs. Consequences of unidentified DDIs include patient harm, HCV treatment failure and resistance emergence, along with inadequate management of patient co-morbidities. In the case of patients with epilepsy, particularly those prescribed multiple AEDs, this study identifies that DDIs are frequent and their management can become complex.

AEDs account for a significant number of potentially severe DDIs with HCV DAAs, with more than one third of patients in this sub-study found to be at risk of a potentially severe DDI which may lead to HCV treatment failure. Given that current first line therapies for focal seizures, the most common seizure type, include carbamazepine and oxcarbazepine, which are both contraindicated with all available DAA regimens, our findings highlight the potential for severe DDIs in a significant proportion of patients with epilepsy as they progress to HCV therapy (233, 254, 301, 302).

Among cases at risk of potential severe DDIs within this study cohort, a statistically significant increase in length of time from HCV treatment assessment to HCV treatment initiation was identified. This is in part due to the level of specialist MDT teamwork required to prepare these patients to start HCV therapy that will be safe and effective. Given the morbidity and mortality risk associated with uncontrolled epilepsy, all AED adaptations within this study were completed under the guidance of neurology specialists. Other factors which contribute to this time lag include, availability of neurology services, the slow tapering of AED regimens required to ensure patient safety when AED regimens are altered, and to ensure the wash out period for enzyme inducing drugs has been observed.

Given the statistically significant increase in time to HCV treatment initiation noted among patients prescribed AEDs at high risk of severe DDI (e.g. carbamazepine), accurate and timely identification and management of potential DDIs at an early stage of patient HCV assessment is of paramount importance to ensure prompt initiation of optimum HCV treatment in epilepsy patients. Multiple successful DDI management strategies may be utilised as highlighted in this study. However, in the majority of cases in this study, given the severe nature of potential DDIs, the interacting AED must be stopped and or replaced within the patients' AED regimen, which can be a slow process.

This study also highlights two patient cases where HCV treatment initiation has been delayed due to AED regimen complexity. Though a small number among the total HCV patient population, epilepsy patients requiring on-going treatment with AEDs which are potent inducers of CYP 450 isoenzymes and drug transporters represent a patient group with no licensed treatment options to date. Three publications in the literature, have reported the use of high dose DAAs to overcome the impact of these potential DDIs in the treatment of seven patients (255, 256, 303). In these reports the DAA regimen utilised was sofosbuvir and high dose daclatasvir, with DAA TDM employed. AED regimens were unchanged throughout HCV treatment and SVR was achieved in all

cases, however TDM did identify reduced daclatasvir maximum and trough plasma concentrations (255). While these studies are valuable in beginning to investigate DAA dosing strategies for co-administration with potent enzyme inducers (e.g. carbamazepine), without the widespread availability of a pharmacokinetic assay to complete TDM, in addition to the heightened cost of high dose DAA therapy, this treatment strategy may only be available in limited settings. In addition, many DAA regimens now employ fixed dose DAA combination preparations which will restrict the ability of clinicians to individualise DAA dosing based on DDI management strategies. Further robust pharmacokinetic studies are required to provide dosing guidance with current DAA therapies.

This study suggests a high rate of clinically significant DDIs between DAAs and AEDs in patients with epilepsy, with management of DDIs impacting on time to initiation of HCV treatment for patients prescribed enzyme inducing AEDs, including phenytoin, phenobarbital, carbamazepine and its derivatives. Pharmacist-led medication reconciliation and DDI assessment aided the identification and management of potentially severe DDIs at an early stage in the HCV patient care process to ensure optimum HCV treatment outcomes for this patient group. The challenge of DDIs will continue to be part of HCV treatment for patients with epilepsy in the future as newly licensed regimens display a similar pharmacokinetic profile to those prescribed in this analysis. More pharmacokinetic studies to guide DAA dosing along with access to pharmacokinetic assays are needed to aid clinicians in optimising HCV treatment choice for this patient cohort who have limited epilepsy management options.

4.5. Pharmacist-led interventions as part of the Hepatitis C model of care

The role of the pharmacist in optimising HCV treatment outcomes, rooted in the evidence generated as part of the studies undertaken in phase one of this research project, provide a strong justification for the role of the pharmacist in HCV patient care but also the importance of the specific process that they complete. The study findings of all four studies, completed as part of phase one of this research project (medication reconciliation, DDI assessment and management, CAM usage assessment and the subset of patients with epilepsy), provide justification for inclusion of medication reconciliation and DDI assessment and management as essential components of the complex intervention toolkit. These two pharmacist-led interventions provided the basis for the formative structure of work that was undertaken in phase two of this project. The findings of these phase one studies underpinned our ability to develop a toolkit that would facilitate a devolved model of HCV care in the Irish healthcare setting and internationally.

It is key that any patient initiated on HCV therapy does not have the efficacy and safety of the treatment impacted negatively by a DDI. The consequences of not completing medication reconciliation and DDI review include, the potential for an unidentified DDI to cause patient harm, HCV treatment failure and resistance emergence along with inadequate management of patient co-morbidities. Once identified the majority of DDIs are manageable either by dose adjustment, switching to an alternative medicine from the same therapeutic class or by discontinuing unnecessary medications.

While HIV co-infected patients now possess an equal opportunity for treatment success, their risk of clinically significant DDIs as identified in this study causes them to remain a special population during the pre-treatment assessment phase. Patients with epilepsy and cardiovascular disease are other examples of special DDI populations identified in this study. Doctors, pharmacists and nurses

involved in the care of HCV patients with these co-morbidities must consider the risk of a potential DDI with all DAA treatment options.

As the numbers accessing DAA based HCV therapy increases worldwide the challenge is to provide realistic guidance that enables health care professionals to make clinical decisions about altering co-medications. The availability of real world DDI evidence in the setting of DAA therapy will aid clinicians in decision making and ensure optimum SVR outcomes are achieved. While the selection of licensed DAAs expands pre-treatment DDI assessment remains a key part of optimising patient and HCV treatment outcomes. References sources to gain information on general or more specific drug interactions with DAAs are continually growing and developing, none more so than the University of Liverpool website www.hep-druginteractions.org (233).

With multiple DAA regimens now licensed, pre-treatment pharmacist assessment, including medication reconciliation and DDI review is key, in ensuring that all patients achieve their potential SVR outcomes without hindrance due to inaccurate or incomplete medication histories or unidentified DDIs (216). The findings of these studies assessing the outcomes of the medication reconciliation and DDI identification and management processes among HCV patients highlights that these processes must be considered for inclusion in any new models of care of interventions developed to expand or devolve HCV care services.

The findings of these studies also re-enforce the importance of the clinical pharmacist as a member of the MDT providing care for patients with chronic HCV infection. The presence of the pharmacist within the MDT is beneficial to both the clinician and the patient as they ensure appropriate DAA prescribing while also educating and counselling the patient about their HCV treatment, providing them with the greatest opportunity for SVR attainment. Pharmacists ensure compliance with treatment guidelines, dispense medications, advise on the management of adverse effects and

monitor and provide advice on patient medication adherence (22). Through these activities the pharmacist using their unique skill base has multiple points of interaction and positive impact on the HCV patient care pathway at the individual patient level.

4.6. Hepatitis C Pre-treatment pharmacist assessment complex intervention toolkit

While we now possess the medications required to eradicate HCV infection, we are lacking scalable intervention-based models of care for all patients to reap the benefits of these curative treatments. There is widespread recognition that research is required to identify evidence-based interventions which can be incorporated into an expanded model of care for HCV to more effectively and efficiently deliver treatment and maximise patient outcomes.

This project aimed to add to the body of evidence-based healthcare interventions which could positively contribute to HCV patient care in Ireland and internationally across all models of care. The research findings from phase one studies have affirmed the hypothesis that pharmacist-led activities have a positive impact on HCV patients treated with DAAs, in promoting patient safety and treatment efficacy through medication reconciliation and DDI review. The phase one studies, which reported the beneficial impact of both medication reconciliation and DDI assessment and management, form the basis of the complex intervention toolkit structure as critical patient care processes in HCV PTPA. The pharmacist plays an important role in HCV PTPA to ensure safe and effective therapy. The findings of this research indicate that PTPA is an essential part of the wider HCV model of care. In this rapidly changing therapeutic landscape, the model of care for HCV is constantly developing and evolving to best serve the patient populations requiring treatment. This includes a devolvement of care beyond specialist centres and specialist prescribers. Regardless of treatment setting, patients must be able to engage with healthcare providers with treatment knowledge and adequate resources to ensure they receive optimum HCV therapy. This project endeavoured to assess the potential impact of a PTPA complex intervention toolkit on the process of patient assessment for HCV treatment.

Why is this PTPA intervention toolkit complex?

1. Pre-treatment patient assessment involves several interventions combined.

2. There are a range of possible outcomes depending on patient, viral factors and optimal treatment recommendations.
3. Multiple HCPs are involved in the pharmaceutical care of HCV patients including doctors, nurses and pharmacists across a wide variety of care settings. (Multiple grades within each HCP may also be involved adding even more complexity)

This project utilised the UK MRC framework for systematic development of the complex intervention toolkit (262, 267). As detailed earlier, there are several other framework options. The MRC framework was chosen as it allows investigation of the context, the intervention and the evaluation to be conducted simultaneously rather than sequentially, which is more reflective of the dynamic and ever-changing process of the complex intervention design process. The MRC framework recommends the use of both quantitative and qualitative methodologies in the design of an intervention, as evidenced in this work.

The development of a process map was the formative step for the development of the intervention toolkit. This qualitative narrative assessment of the pharmaceutical care tasks involved HCV patient care, along with the phase one study data, formed the basis for the initial development of the complex intervention toolkit.

4.6.1. Selection of components of the PTPA toolkit

Patient Baseline Characteristics

Part 1 of the toolkit involves the identification and documentation of specific patient characteristics. Process mapping identified the importance of initial baseline patient characteristics review. This section was further developed and formalised using the expertise and HCV knowledge of the researcher and the stakeholder research group. The aim was to collect all necessary

characteristics that were deemed relevant to completing a HCV patient assessment without overburdening the user.

Multiple patient factors were identified meriting consideration including, liver fibrosis staging and determination of cirrhosis status, patient co-morbidities (e.g. HIV, diabetes, epilepsy, HBV infection), duration of HCV infection and route of acquisition. While DAAs have few if any contraindications to use, it is still essential to obtain a full picture of patient co-morbidities and how they may impact a patient's ability to comply with and complete HCV treatment safely and effectively. Underlying depression can affect adherence to HCV treatment in some patients and this factor should be considered in all patients with co-morbid depression being assessed for treatment (22). Another example relates to patients who are co-infected with HBV. Given the confirmed risk of potential reactivation of HBV infection in patients treated with DAAs, it is key that patient HBV status is confirmed prior to treatment and the complex intervention toolkit prompts users to review this (60, 61).

In patients with cirrhosis, the extent of existing hepatic dysfunction and the presence of decompensation must be determined to allow accurate staging of liver disease. The toolkit guides users to complete the CTP and MELDNa scores. Liver disease staging is a key assessment in terms of time to treatment and in relation to DAA regimen choice as HCV protease inhibitors (e.g. glecaprevir, voxilaprevir) are contraindicated in patients with current or previous hepatic decompensation (CTP B or C cirrhosis) (60, 61). This is due to the potential for significant increases in the bioavailability of protease inhibitors in this patient group and thus a significant risk of adverse drug effects which have the potential to trigger further hepatic decompensation and can be fatal. Inclusion of a requirement for information relating to liver imaging as part of the toolkit is aiming to make the toolkit user aware of ultrasound HCC surveillance occurrence and to ensure this

process is in place for all cirrhotic patients on an on-going basis and that the importance of long-term follow-up is not lost after the end of treatment or SVR 12 clinic visit.

These are just a few examples of the benefits of the first section of the toolkit. Collation and review of patient baseline characteristics aims to provide the toolkit user with a clear picture of the patient's health state. It is essential that part 1 is completed first to fully equip the toolkit user to progress to subsequent components of the toolkit.

Medication reconciliation and DDI assessment & management

These sections of the toolkit (part 2 and part 4) involve completion of medication reconciliation which facilitates completion of a DDI review. Evidence collected to develop the theory behind the intervention toolkit included the positive primary evidence from the medication reconciliation and DDI studies which strengthened the basis for inclusion of these two core pharmacist-led components within the toolkit. As previously described, phase one research including medication reconciliation and DDI review identified medication variances among 74% of the study population with 16 variance episodes rated as having the potential to have a significant and severe impact on patient safety by a panel of pharmacists. Following on from medication reconciliation completion, 71% of the patient cohort were identified as being at risk of a potential DDI with proposed DAA therapy. Based on the pharmacist-led interventions completed and described in phase one studies, no patient was identified to have failed HCV therapy due to an unidentified DDI with DAA therapy with a high overall SVR rate reported (92.7%).

These phase-one study findings formed a strong evidential basis for onward development of the toolkit. The findings from the related sub-study assessing the prevalence and type of CAM product use and the importance of CAM identification through medication reconciliation and analysis for DDI risk is a prime example of why these two steps must be included in the pre-treatment

assessment toolkit. The epilepsy DDI sub-study again highlighted the importance of the inclusion of medication reconciliation but also shows the significant DDI risks associated with certain co-medications which can cause treatment failure or co-morbidity mismanagement if undetected and inappropriately managed.

Selection of HCV DAA treatment regimen

There are now multiple potential DAA regimen combinations available worldwide for HCV treatment. Each regimen is associated with various medication combinations, treatment durations, DDIs and potential side effects. Strategic selection of an optimum treatment regimen for each patient is crucial (21). This section of the toolkit collates information specific to the viral infection including genotype, viral load, previous HCV treatment and response, and details of DAA resistance testing, if previous DAA treatment received.

The section of the toolkit is designed to overcome the potential selection of an incorrect treatment duration. For example, for non-cirrhotic patients with genotype 1 infection, the duration of treatment with SOF/LDV can vary from 8 weeks to 12 weeks, depending on prior HCV treatment history and HCV viral load pre-treatment. If too short a course of treatment is selected for an individual patient, the ability to achieve SVR can be compromised. If treatment extends beyond the recommended guidelines, it may expose patients to a greater risk of adverse effects as well as a substantially increasing DAA regimen costs for the healthcare system (21). Of note, even when prescribing is limited to specialist centres, a lack of compliance with international treatment guidelines and product labelling recommendations has led to a sub-optimal treatment outcome for patients (304).

Review of baseline laboratory results which occurs in the first section of the PTPA (e.g. liver function tests, haemoglobin, and creatinine clearance) is also an important part of the regimen selection process, as it allows the PTPA toolkit user to gauge suitability of the DAA regimen and to predict

potential adverse effects that may occur with HCV therapy (22). For example, in patients where addition of RBV to the treatment regimen is being considered, presence of, or risk factors for, anaemia should be assessed along with patient weight and renal function status.

While on-treatment viral load, response guided therapy, is no longer required with currently available DAAs, some regimens do require consideration of previous HCV treatment regimens and resistance mutation assessment, prior to treatment duration and regimen selection. For example, pre-treatment viral load and NS5A resistance mutation analysis are required with the regimen grazoprevir/elbasvir in HCV genotype 1a and genotype 4 patients, to guide the need for addition of RBV, and to determine the optimum treatment duration of 12 versus 16 weeks (305).

Reference to compliance with national treatment guidelines was considered an important point for inclusion in this section also. HCV treatment guidelines were in a continual state of flux during the lifetime of this research project with regular additions of new treatment regimens and removal from use of those which had been superseded. Therefore, prompting prescribers to review the most up to date treatment guidelines on a regular basis is an important step, especially with regard to treatment duration. Given that DAA pricing is based on annual or multi-annual budget planning on a national level in most countries, including Ireland, HCPs who are assessing and prescribing DAA therapy must comply with guidelines. Ensuring cost effective medicines usage is another core component of pharmaceutical care in HCV patients.

4.6.2. Stakeholder research group

The role of the stakeholder research group was to refine the toolkit to ensure that it was fit for purpose. The stakeholder research group completed nine reviews of the draft complex intervention toolkit. This served to cement the core components of the toolkit. The importance of stakeholder involvement from these initial stages of the complex intervention toolkit development cannot be

overstated. As the stakeholders represent future toolkit users, they were continually assessing user-friendliness, readability, process flow, issues that may arise with use of the toolkit in different healthcare environments and in different contexts. The stakeholder research group also identified guiding principles for the toolkit development, which were followed through all steps of the toolkit development and optimisation.

While the components of the toolkit were reported as separate sections in the results, they ultimately come together to provide one cohesive intervention toolkit that takes the user from initial patient baseline characteristics review, through medication reconciliation and DDI review to HCV regimen selection and DDI management planning (Appendix 26).

4.6.3. Logic model

The logic model served to refine the complex intervention model by identifying important influences on PTPA toolkit use and outcomes, relations between components within the toolkit and also the levels within the healthcare system that will utilise it, and any consequences not previously considered as part of the nine rounds of stakeholder review. The logic model also aided research project planning as it highlighted resource needs for assessment and implementation of the toolkit. It is important to be aware of, and consider, all levels within a healthcare intervention process as a decision to implement a change at one level could be cancelled out or encouraged by actions at other levels. In this case of the PTPA toolkit, its design is aimed at ensuring patients that do engage in any model of HCV care receive an optimum HCV treatment regimen. However, it is reliant on co-development of interventions to improve patient engagement with HCV services and to expand the model of HCV care out into community settings where patients requiring HCV treatment are located.

4.6.4. Context

To understand how an intervention might operate and how a system will respond, an understanding of the context of the system that it is being introduced into is vital. Context includes anything external to the intervention that may act as a barrier or facilitator to its implementation, or its outcomes. An intervention may have different effects in different contexts even if its implementation does not change. What works in one setting may not be as effective elsewhere.

The stakeholder research group provided a significant depth and range of knowledge around HCV care provision in Ireland across all areas of the healthcare service. Review of the toolkit by this group provoked discussion on how the intervention would be delivered across what is a very varied healthcare service in terms of available resources, including staff experience, profession and skill mix, clinic space, technology and healthcare setting (tertiary or primary care). The main point of discussion around context of use was the potential for variation across healthcare settings due to staff skill mix, level of staffing and time to complete assessment. As the toolkit aims to serve as both an assessment toolkit and education toolkit, this helps in part to overcome the different skill and experience levels. Indeed, given that the toolkit proved effective among both doctors and pharmacists in the evaluation study, this demonstrates that it can be of use among different healthcare professional groups. The content of the toolkit should also be reviewed prior to adoption in a new treatment setting. For example, if there is no access to a fibroscan and staging is to be based on APRI or FIB-4 results then the baseline patient characteristics section and liver staging sections should be adjusted to reflect this. Conversely, in a community setting with access to a fibroscan and DBST to confirm viremia, treatment may occur in non-cirrhotic patients without completion of blood tests. This would require removal of the blood results section from the baseline characteristics profile. Concerns over time to completion of patient HCV assessments were alleviated by the findings of the evaluation study which found no statistically significant difference

in time to completion of patient assessment with and without the toolkit among the pharmacist and clinician groups.

Another issue that may arise in different treatment settings or contexts of use, is access to patient information required to complete the patient assessment, using the PTPA toolkit. One solution to this may be the development of an electronic version of the toolkit and the completion of different sections by different HCPs, at different centres, and sharing of information via an electronic platform. Alternatively, a HCV treatment programme may adapt the PTPA toolkit to capture information that is readily available and insert safety stops or limit the treatment options to overcome the information deficits, without compromising HCV treatment outcomes and patient safety.

The availability of the toolkit aims to facilitate treatment assessment and initiation by a wider team of HCPs, who provide care to patients from all sectors of society, in a wide variety of care settings and locations. A significant strength of the toolkit is its adaptability in the setting of different contexts of use. This can help to overcome patient specific factors which currently hinder access to treatment. Many patients are not linked with HCV treatment services in the tertiary care model due to fear of discrimination or stigma, poor social circumstance, a lack of trust in hospital services or poor health literacy. The toolkit, by supporting the local healthcare providers of marginalised patient groups to assess and treat in community the toolkit, is overcoming the limitations of a specialist-based service.

In addition, circumstances may change through the lifecycle of a study which may impact the context of use of the complex intervention. For example, over the course of this research project, pangenotypic DAAs became available which meant genotype testing was not essential if access to these pangenotypic agents was permitted. However, given the significant cost impact of widespread pangenotypic regimen prescribing, their use in the Irish treatment model was

restricted. So therefore, while initially genotype could have been removed from the toolkit as a required piece of information, use of the toolkit in the Irish setting necessitates its inclusion and consideration in prescribing decisions.

4.6.5. Feasibility and Piloting

This component of the toolkit development focused on optimising the individual sections of the intervention toolkit. Optimisation is a critical step in the development of complex interventions that cannot be overlooked. A strength of this study was the use of both quantitative (pilot study) and qualitative (focus groups and interviews) study methods to guide optimisation of the PTPA toolkit. The stakeholder group, logic modelling and feasibility studies all represented prospective optimisation strategies (260).

Both feasibility and pilot testing were used to identify any issues with the toolkit among HCPs prior to the evaluation study. The toolkit was perceived to have the potential for use across a variety of settings, helping to overcome some of the current barriers that prohibit marginalised patient populations from engaging in HCV treatment. It is designed to ensure that if the intervention progresses to full-scale evaluation that it contains the “best ingredients”, as determined by developing the intervention using the MRC framework and ensuring that multiple techniques are employed to optimise the intervention.

The focus groups and interviews highlighted some HCP perspectives on the need for an expanded model of care with more integration of services between the community and hospital settings. Overall perceptions of complex interventions in healthcare and specifically in HCV care were positive. Participants displayed good knowledge around toolkit use. Positive feedback was received from participants in terms of toolkit use aiding their education and learning, particularly around the areas of DDIs and cirrhosis assessment, which are core parts of the PTPA toolkit. Potential barriers

to use identified included time to complete assessments using the toolkit, and access to all the required information. Another barrier to widespread implementation of the toolkit highlighted was the potential that certain HCPs may feel that their implicit knowledge and sense of the appropriate treatment is more or just as accurate as the toolkit and therefore they may not follow the intervention toolkit pathway.

Completion of the pilot study led to the conclusion that the PTPA complex intervention toolkit did positively impact optimum DAA regimen selection. These findings confirmed the decision to progress to evaluation of the toolkit. The evidence from the pilot study supported the progression of the toolkit to evaluation.

4.6.6. Complex intervention toolkit evaluation

The wider effectiveness and acceptability of the intervention was assessed through a matched cohort evaluation study with three distinct groups of HCPs. (i.e. pharmacists, nurses and clinicians)

The evaluation study identified that the intervention toolkit had a significant positive effect in terms of improving HCP selection of the optimum DAA treatment regimen among both pharmacists and doctors, as compared with current standard of care. Within the pharmacist group toolkit use resulted in the selection of the optimum HCV treatment regimen in 93.8% of cases as opposed to 60.9% of cases in the standard of care arm ($p < 0.05$). Similarly, within the clinician arm, toolkit use was associated with selection of optimum HCV treatment in 82.1% of cases, compared with 68.8% of cases completed without the toolkit ($p < 0.05$).

In the nursing arm of the study, while there was a trend towards an increase in the rate of optimum HCV treatment regimen selection using the toolkit, on analysis this was not found to be a statistically significant improvement, as compared with current standard of care ($p: 0.148$). This

finding among the nursing study cohort may reflect the nurse roles and responsibilities in the HCV care pathway in Ireland. In practice they are heavily involved in screening patients, providing education, completing patient assessments, including fibroscan and monitoring patients on treatment. As the model of care for HCV in Ireland using DAAs is resourced with clinical pharmacists at each treatment site, the nursing staff may not always participate in, or consider, the choice of DAA regimen. In comparison, use of the toolkit among doctors and pharmacists triggered a significant increase in selection of an optimum HCV treatment regimen which indicates that both HCP groups could benefit from availability of this toolkit in their everyday practice.

The rate of detection of DDIs increased with toolkit use among all three groups of HCPs and was found to be statistically significant. DDI identification and management is a key part of safe and effective HCV patient care. The initial research completed as part of this project highlighted the potentially significant negative effects of unidentified or mismanaged DDIs. Even if HCPs who identify DDIs using the toolkit are unsure of how to manage them, once identified they can utilise the MDT structure of the HCV care team to gain advice and information on how to manage the DDIs appropriately. For the detection of DDIs using the toolkit, the ICC among study participants was excellent which gives a good indication that agreement among toolkit users was high, adding weight to the positive association of toolkit use to optimum DAA regimen selection.

The rate of patient interventions identified by HCPs increased across all study arms with use of the PTPA toolkit. However, the association between use of the toolkit and identification of patient interventions was only found to be statistically significant among the pharmacist group (PTPA toolkit users proposed an average of 2.6 interventions per test case versus 1.8 interventions per case using standard of care). Among all groups the ICC for this outcome was low indicating a wide variation within study groups in terms of the number of interventions identified relating to specific

test cases. This finding warrants further investigation to determine HCP factors and toolkit factors which may be impacting this outcome measurement.

One factor which was broached as a potential barrier to implementation through both the stakeholder research group and the feasibility study was the length of time toolkit use would take, as compared with current standard of care. While use of the toolkit was associated with a longer time to completion of test cases as compared with standard care this was only found to be statistically significantly longer among the nursing group. In addition, when the positive outcomes of PTPA toolkit use in terms of optimum DAA regimen selection and DDI detection are taken into consideration, the increase in time appears justified.

4.6.7. Survey on acceptability of the PTPA complex intervention toolkit implementation

This survey allowed further assessment of the potential uptake of use of the PTPA complex intervention toolkit among HCPs. This piece of qualitative research acted as a process evaluation building on previous qualitative data collection completed as part of the complex intervention toolkit design, development and optimisation stages. Gaining feedback post intervention testing in this way is considered retrospective optimisation (260).

Survey results identified that implementation of the PTPA complex intervention toolkit within the HCV model of care was feasible and acceptable among all grades of HCPs, and was identified as having the potential to enhance staff education and the rate of completion of patient HCV treatment assessments.

4.6.8. PTPA Complex intervention toolkit implementation

The PTPA complex intervention toolkit was developed and tested through the rigorous MRC framework and displayed efficacy as part of an evaluation study. Given the positive findings of the

PTPA complex intervention toolkit evaluation, the study data was presented to the Irish National HCV treatment programme in 2018.

The positive findings of this PTPA toolkit evaluation study will now see it progress to use by doctors and pharmacists as part of the Irish National Hepatitis C Treatment Programme community treatment project. The intervention toolkit is also standard of care within the pharmacy service at St. James's Hospital and is being developed into an electronic note format for the St. James's Hospital electronic prescribing platform which may be used by both doctors and pharmacists. The toolkit has been made available to all hospital-based HCV treatment clinics and also to HCV clinics with the drug treatment services.

Roll-out of the educational component of the PTPA toolkit as part of the National Hepatitis C Treatment Programme Community Treatment pilot has commenced with three sessions to date. Roll-out of the educational component with the Irish Pharmacy Union, the professional body representing community pharmacists in Ireland is in planning.

4.7. Interpretation of complex intervention toolkit study findings

Few interventions are truly simple, especially in healthcare. Therefore, it is not surprising that complex interventions are widely used in healthcare settings. They facilitate HCPs in making clinical decisions related to patient care.

Ultimately the aim of this research project was to assist HCPs, whether they are doctors, nurses or pharmacists, across all grades, to make the right choice in terms of DAA prescribing, regardless of the treatment setting. The findings of this evaluation study confirm the effectiveness of the PTPA toolkit in aiding doctors and pharmacists in selecting optimum HCV treatment.

For a reliable assessment of the results of this evaluation, it must be reviewed in the context of other studies of similar interventions, if they exist. Research studies published to date have looked at ways to increase access to HCV care via specific community routes and have compared treatment uptake rates to tertiary specialist care. There is much focus on providing alternative routes of HCV treatment access beyond specialist centres but little if any description of how patients identified are assessed for HCV treatment in these expanded treatment settings. No study to date has investigated the development and evaluation of a pre-treatment assessment complex intervention toolkit which aims to ensure optimum DAA treatment selection by HCPs, once patients are recruited into HCV care, regardless of the treatment setting. The PTPA toolkit harnesses the evidence-based interventions which occur at the specialist HCV service level and presents them in a user-friendly format for non-specialist HCP prescribers to utilise in an expanded model of care.

Previous research examining interventions aimed at devolved HCV care included use of telemedicine, harnessing of existing OST services and use of outreach HCPs (96, 121, 159). One research group has looked at designing and developing a complex intervention aimed at upscaling treatment beyond specialist tertiary centres. This research has been undertaken by Radley *et al* within the Scottish Hepatitis C treatment programme (104, 193, 194). This complex intervention couples DBST and subsequent HCV treatment, if required, in conjunction with provision of OST via a patient's community pharmacy. This complex intervention also followed the MRC framework for development. Of note, this study was limited to genotype 1 patients and all patients were treated with SOF/LDV which meant that no decisions were required by the participating pharmacists in terms of regimen selection (104, 193). No other pharmacist-based research has examined the development of an HCV pre-treatment assessment complex intervention toolkit to aid prescribers in the process of assessing and treatment patients.

During the lifetime of this research project several online or mobile phone applications (apps) or tools have been developed, which state that they aid prescribers in selecting the appropriate DAA regimen for their specific patient. The EASL HCV advisor app® is a tool developed by EASL to aid clinicians when choosing which HCV DAA regimen to prescribe. However, both the EASL HCV advisor app® and Swiss Advisor App® (upon which the EASL app is based) only consider a limited number of patient characteristics, namely, HCV genotype, fibrosis staging, previous treatment experience, patient weight, renal function and DDIs. The HCV therapy selector app® considers even less information, requiring only patient genotype, fibrosis staging and previous treatment experience. This app then provides you with tables of study outcome information for multiple regimens. Within each choice, detail is provided on adverse effects and a link to the University of Liverpool DDI website is provided. While these tools provide excellent and invaluable information in an easy to use format, they are only part of the answer in a HCV patient assessment.

Another important difference between these tools and the PTPA intervention toolkit is the intensity of the intervention. PTPA toolkit users were provided with an education and training presentation, and a comprehensive DDI reference list. The PTPA toolkit also incorporates a patient characteristics and medication reconciliation checklist.

4.7.1. Education and training of HCPs as HCV models of care change

A US study by Thomson *et al* conducted in 2015 identified that among study survey responses, 70% of clinicians self-reported that they did not feel their knowledge of HCV DAA-based treatments was up to date (162). Respondents were working in internal medicines, family practice and paediatrics. Only 36% of study respondents were aware that SVR rates had the potential to be greater than 90% (162). A similar proportion were also unaware that DAA treatment was an all oral medication regimen (162). Only 13% of respondents who considered themselves knowledgeable about HCV reported that they would feel comfortable treating non-cirrhotic patients for HCV in their clinic

setting (162). While knowledge will have increased since 2015, this survey data highlights the valuable point that for many primary care HCPs who will be requested to participate in community treatment programmes as part of national HCV treatment plans, there will be a significant knowledge gap which needs to be bridged. It is noteworthy that few if any of the studies published relating to movement of HCV care beyond specialist centres provide any information on how healthcare staff in these settings were provided with education or training to be competent and confident to actively participate in these projects of devolved HCV care.

One Australian community consultation pathway study reported the use of a paper-based remote consultation proforma, development of an information page with links to guidelines and provision of a peer-led education session for GPs (136). The ASCEND study by Kattakuzhy *et al* reported the provision of one three-hour training session to the prescriber participants (145). While the study, which comprised 600 patients noted high rates of SVR among its cohort, inclusion criteria meant that again only genotype 1 infection were recruited and again the only permitted regimen for prescribing was SOF/LDV (145). This meant that the key step of regimen selection was removed from the decision-making process of the community-based prescriber. This represents an oversimplification of the real-world clinical practice setting. In addition, post-study analysis identified that 90% of the total patient cohort received a 12-week course of treatment when in fact 306 patients within the study cohort fit the criteria for a shortened 8-week course. Over treating a significant proportion of a real-world cohort in this way would have significant budget and potential patient safety implications. It also counters the idea that providing community treatment means more patients will be treated. If for example a prescriber workload dictates that he has 30 HCV patients on DAA treatment at any one time, if treatment for a significant proportion of these patients could be shortened then the prescriber will treat more patients in a shorter period of time with the same resources. In addition, there was no detail given in this study on how and if DDI issues were managed (145).

Other published studies provide little detail on how HCPs providing care in these devolved care models were trained or upskilled to perform their roles (104, 153, 193). No published studies report use or development of standardised interventions to help HCPs such as that developed as part of this research project. Regardless of the model of care chosen, a key part of successful adoption of any model are the interventions and tools provided to the HCPs to assist them in completing patient HCV treatment assessments. There is a need to better describe the HCP education and training behind newly developed complex interventions.

The PTPA toolkit offers users a comprehensive checklist and education support as they complete patient HCV assessments. A key point highlighted by the study participants was that use of the PTPA toolkit could improve HCP confidence when completing HCV patient assessments, regardless of the care setting. As such, the PTPA complex intervention toolkit would serve as an intervention to overcome barriers to HCV patient assessment among HCPs. This could also lead to an increase in the number and quality of assessments that HCPs complete over time and ultimately the number of patients they initiate on HCV treatment. Even if among a devolved treatment model, a non-specialist only managed to treat 1-2 patients per month with the help of the toolkit, if they are also learning and being educated about screening and signposting of specialist services for patients then this adds to the impact potential of the PTPA toolkit. The PTPA complex intervention toolkit is about harnessing the skill base of non-specialist HCV care providers and empowering them to engage more with the patient assessment and treatment pathway.

4.7.2. Proposed utilisation settings for the PTPA toolkit

The toolkit has the potential for broad ranging use across all types of models of care whether it be devolved community treatment or a shared care treatment programme between hospital specialists and community healthcare workers. This toolkit needs to be used in conjunction with

other evidence-based interventions which increase patient diagnosis and linkage to a prescriber who can then use the PTPA toolkit to assess patients for HCV treatment and ultimately initiate an appropriate treatment regimen.

Given that a recent European patient survey identified that only 20% of patients had access to DAA treatment in a non-hospital setting, the positive findings of this design, development and evaluation study for the PTPA complex intervention toolkit is even more significant (306). Treatment in the community setting has been shown to be feasible (154, 193). This toolkit has the potential to be integrated into many different forms of HCV care settings, whether it be a GP practice, a hospital community outreach unit, hospital and community shared care models or community pharmacy-based patient assessment and treatment.

Community based HCV treatment/General practitioners

Given the positive findings of PTPA toolkit use among doctors who participated in the evaluation study, use of the toolkit among GPs has the potential to provide education and increase their ability to assess patients for HCV treatment whether that be as an independent prescriber or as part of a shared care model. Creating interventions that facilitate GPs to confidently assess and treat patients for HCV is a positive intervention to upscale HCV treatment rates. GP-based treatment allows patients to be treated within an existing trusting patient-clinician partnership. This is a key benefit for marginalised patient populations including those experiencing homelessness and patients in addiction. Injecting drug use is the most common mode of HCV transmission and therefore to bring about a significant reduction in HCV incidence and prevalence, interventions which specifically target this patient group are needed.

A community-based MDT model has been explored as part of research into devolved HCV care. Such an MDT which incorporates clinicians, pharmacists, nurses, social workers, dieticians,

psychiatry and peer support teams or community-based advocates has the potential to successfully engage marginalised patient groups within a broader HCV treatment model. The PTPA toolkit could be utilised by such a service as part of training or in practice by the HCPs completing patient assessments. One example from Sims *et al* describes the functioning of an outpatient MDT helping to treat poor and uninsured patients in the US (118). In a recently published meta-analysis, the involvement of multidisciplinary teams positively correlated with SVR rates in a multivariable meta-regression analysis (307).

Community pharmacists

The potential for community pharmacy practices to make a greater contribution to the health of their local populations has been recognised for some time (308-310). Community pharmacies have a wide population reach and are a free advice service, with daily opening hours and no requirement to make an appointment. Patients consistently rate pharmacists as one of the most trusted healthcare providers. For most patients, community pharmacies represent a familiar and unthreatening environment. Community pharmacists have existing relationships and trust built up within their communities and have existing links and relationships with PWIDs in the community through OST dispensing and needle exchange programmes. Pharmacists have long had a major role in delivering OST to patients in the community with a high prevalence of HCV, and pharmacist involvement in delivering HCV treatment through multi-disciplinary clinics has been described for some time (180, 181). The delivery of HCV testing and treatment through community-based care pathways has also been shown to be feasible (102, 194, 311). Given the central role of community pharmacists in primary healthcare their potential to participate in HCV community treatment initiatives should be further explored. The potential for pharmacists working in all practice environments in Ireland to make a robust contribution to HCV treatment, can be supported using this PTPA toolkit. In addition, the community pharmacy setting, with some adjustments, offers an environment that is amenable to point of care testing as has been shown by UK studies (130, 194).

Pharmacies are already completing tasks such as BP monitoring, blood sugar checks and flu vaccinations. This type of capacity building is key to upscaling the model of care to achieve elimination targets.

While these examples of devolved or shared care models may work well, no one model of care will meet the needs of the heterogeneous HCV patient population. A combination of service types and variations in the model of care need to be provided to ensure screening, diagnosis and treatment is accessible to all patients.

4.8. Conclusion

This research project has endeavoured to incorporate pharmacist interventions into a complex intervention toolkit to aid optimum HCV patient assessment across all models of care. Refinement of the pharmacist-led pre-treatment intervention process and its development into a validated PTPA complex intervention toolkit will promote appropriate and quality driven pharmaceutical care of all patients treated for HCV infection across any model of care. This study provides a novel approach to expanding the model of care in the field of HCV treatment and represents an important contribution to the limited data surrounding complex intervention development for use in the area of HCV patient care. The research project links with two of the WHO recommendations in the target for HCV elimination, namely, simple and standardised algorithms across the continuum of care and development of data systems to monitor the quality of individual care and the cascade of care (4).

As our model of care for HCV develops and evolves there is the potential for treatment programmes to expand in order to include community-based access to treatment. Evidence-based interventions such as the PTPA should be strategically incorporated into HCV treatment implementation efforts to most effectively deliver treatment and maximise treatment outcomes. The PTPA complex intervention toolkit is a novel intervention incorporating all aspects of the pre-treatment assessment process to ensure optimum pharmacotherapy for all HCV patients in Ireland across the continually expanding model of care, which strives to achieve HCV eradication. Development and use of this type of complex intervention toolkit model should be considered for application in other clinical disciplines.

4.9. Future research

- On-going dissemination of the research findings at a national and international level, will be undertaken, through the submission of papers for journal publication, highlighting the value of the project results to decision makers, to facilitate adoption in HCV treatment settings across all models of care.
- Development of an electronic format of the PTPA intervention toolkit for incorporation into the hospital electronic patient healthcare record and exploratory work on incorporation into primary care GP prescribing software applications.
- Economic evaluation of the PTPA toolkit: This will initially involve a micro-costing study to determine the costs associated with the implementation of the toolkit using a time-in-motion study, followed by a cost-effective analysis comparing outcomes from PTPA toolkit use compared with no intervention.
- The experience and positive outcomes from the PTPA toolkit development process have the potential to be applied to other chronic disease states in the infectious disease setting and in non-communicable disease states.

4.10. Research Outputs

2019

Research Journal Publications

- Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Pharmacist-led pre-treatment assessment, management and outcomes in a Hepatitis C treatment patient cohort.

International Journal of Clinical Pharmacy. 2019 Jul 11. DOI: 10.1007/s11096-019-00876-6

Conference Poster Presentations

- *European Association for the Study of Liver Diseases (EASL) International Annual Conference April 2019, Vienna, Poster Presentation: Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. THU-392: Building capacity within a hepatitis C treatment model. the validation process for a hepatitis C pre-treatment pharmacist assessment complex intervention toolkit. [Awarded EASL conference registration bursary.](#)*
- *Hospital Pharmacists Association of Ireland Annual National Conference 2019 Poster presentation: Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Healthcare professional perceptions and opinions on the use of complex intervention tools in healthcare and their potential for use in Hepatitis C patient care.*
- *Hospital Pharmacists Association of Ireland Annual National Conference 2019 Poster presentation: Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Building capacity within a hepatitis C treatment model. the validation process for a hepatitis C pre-treatment pharmacist assessment complex intervention toolkit. [Awarded 2nd Prize in the Research Category.](#)*
- *Infectious Diseases Society of Ireland (IDSI) Annual National Conference 2019 Poster presentation: Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Building capacity within a hepatitis C treatment model. the validation process for a hepatitis C pre-treatment pharmacist assessment complex intervention toolkit.*

- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2019, Poster Presentation.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Building capacity within a hepatitis C treatment model. the validation process for a hepatitis C pre-treatment pharmacist assessment complex intervention toolkit.
- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2019, Poster Presentation.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Healthcare professional perceptions and opinions on the use of complex intervention tools in healthcare and their potential for use in Hepatitis C patient care.

2018

Publications

- *Irish Pharmacy Union: Design, development and presentation of an online educational module on Hepatitis C for pharmacists working in the community pharmacy setting.*

Conference Oral Presentations

- *HCV 2018 International Conference, Dublin, October 2018.* Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Global Challenges: International and national approaches to prevention, treatment, eradication and related viral threats.
- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Hepatitis C Pre-Treatment Pharmacist Assessment: the development & optimisation process for a complex intervention toolkit.
- *Irish Hepatology Nurse Association Spring Meeting.* Coghlan M. EASL outcomes: Adapting HCV treatment algorithms for all cohorts.

Conference Poster Presentations

- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Assessment of the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit.
- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Hepatitis C Direct-Acting Anti-Viral (DAA) treatment options in patients with epilepsy. A drug -drug interaction dilemma in chronic Hepatitis C (CHC) infection.
- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Coghlan M, McCarthy S, Melanophy G, O'Dwyer M. An Analysis of the Medication Reconciliation Process in an Outpatient Clinic Setting.
- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Coffey J, Coghlan M, Melanophy G, Bermingham M. A study to describe and assess the appropriateness of medications prescribed in cirrhotic patients using a resource toolkit.
- *Hospital Pharmacists Association of Ireland Annual National Conference 2018.* Kelly M, Coghlan M, Bannan C, Farrell G, Broderick M, Murray C, Melanophy G, Bergin C. The evolving role of ribavirin in HCV treatment – efficacy and safety for management of HCV- mono and HIV/HCV co-infected patients.
- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2018.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Hepatitis C Direct-Acting Anti-Viral (DAA) treatment options in patients with epilepsy. A drug -drug interaction dilemma in chronic Hepatitis C (CHC) infection.
- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2018.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Assessment of the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit

- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2018.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Hepatitis C Pre-Treatment Pharmacist Assessment: the development & optimisation process for a complex intervention toolkit
- *HCV 2018 International Conference, Dublin, October 2018.* Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Assessing the feasibility of the pre-treatment pharmacist assessment toolkit as a strategy to expand the Irish Hepatitis C model of care.

2017

Conference Oral Presentations

- *SPHeRE (Structured Population and Health Services Research Education) Annual National Conference 2017.* Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Hepatitis C pre-treatment pharmacist assessment: the development process for a complex intervention toolkit.
- *All-Ireland Pharmacy Annual Conference October 2017, Oral Presentation:* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Drug-drug interactions of high prevalence in a real-world Hepatitis C treatment setting. Introduction of a novel pre-treatment pharmacist assessment toolkit.

Conference Poster Presentations

- *European Association for the Study of Liver Diseases (EASL) International Annual Conference April 2017, Amsterdam.* Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Drug-drug interactions of high prevalence in a real-world Hepatitis C treatment setting. The implications for patient management.
- *European Association for the Study of Liver Diseases (EASL) International Annual Conference April 2017, Amsterdam.* McGettrick P, Lee J, Coghlan M, Farrell G, Murray C, Broderick M,

Hughes G, Bergin C, O'Connell S. Co-Infection Sustained Viral Response and Antiretroviral Switch in the DAA Era: An Irish Experience.

- *Hospital Pharmacists Association of Ireland Annual National Conference 2017*. Coghlan M, Corbett S, Melanophy G, Henman M. Analysis of the safety and tolerability profile of Hepatitis C direct acting anti-virals in a real-world population
- *All-Ireland Pharmacy Annual Conference October 2017*. Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Hepatitis C pre-treatment pharmacist assessment: the development process for a complex intervention toolkit.
- *American Association for the Study of Liver Diseases, International Annual Conference October 2017, Washington DC*. Coghlan M, O'Leary A, Melanophy G, Bergin C, Norris S. Hepatitis C Direct-Acting Anti-Viral treatment options in patients with epilepsy. A drug-drug interaction dilemma in Hepatitis C infection.

2016

- *Irish Hepatitis C Research & Outcomes Network Pharmacy Research Bursary Competition 2016/2017*: Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. Validation of a Hepatitis C pre-treatment pharmacist assessment complex intervention toolkit. [Bursary application successful](#).

Conference Oral Presentations

- *St. James's Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2016*. Coghlan M, O'Leary A, Melanophy G, Norris S, Bergin C. A description of the prevalence, significance and management strategies for drug-drug interactions with all oral DAA based HCV therapy.

Conference Poster Presentations

- *Hospital Pharmacists Association of Ireland Annual National Conference 2016.* Coghlan M, O’Leary A, Melanophy G, Norris S, Bergin C. DDIs & DAAs: A description of the prevalence, significance and management strategies for drug-drug interactions with all oral DAA based HCV therapy. **Awarded 2nd Prize in the Research Category**
- *Infectious Diseases Society of Ireland (IDSI) Annual National Conference 2016.* Coghlan M, O’Leary A, Melanophy G, Norris S, Bergin C. Always ask about antacids!
- *UK Clinical Pharmacy Association Annual National Conference 2016.* Coghlan M, O’Leary A, Melanophy G, Norris S, Bergin C. DDIs & DAAs: Pharmacist-led management of drug-drug interactions in a Hepatitis C clinic. **Poster highly commended.**
- *St. James’s Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2016.* Coghlan M, O’Leary A, Melanophy G, Norris S, Bergin C. Acid suppressing medications: A study to determine their prevalence of use and the pharmacist led interventions used to manage the potential for interaction with Hepatitis C direct acting anti-virals.

2015

Conference Oral Presentations

- *St. James’s Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2015, Oral & Poster Presentation.* Coghlan M, Kelly S, Bannan C, Farrell G, Broderick M, O’Dea S, Murray C, Bergin C. From Clinical Trial to Real World: Treatment outcomes for DAA based Hepatitis C triple therapy in a HIV co-infection and Methadone Maintenance Therapy population.

Conference Poster Presentations

- *Hospital Pharmacists Association of Ireland Annual National Conference:* Coghlan M, Kelly S, Bannan C, Farrell G, Broderick M, O’Dea S, Murray C, Bergin C. From Clinical Trial to Real World: Treatment outcomes for DAA based Hepatitis C triple therapy in a HIV co-infection and Methadone Maintenance Therapy population.
- *Infectious Diseases Society of Ireland (IDSI) Annual National Conference:* Coghlan M, Kelly S, Bannan C, Farrell G, Broderick M, O’Dea S, Murray C, Bergin C. Interferon Free Hepatitis C Treatments: Experience to date in the co-infection setting.
- *Infectious Diseases Society of Ireland (IDSI) Annual National Conference:* From Clinical Trial to Real World: Treatment outcomes for DAA based Hepatitis C triple therapy in a HIV co-infection and Methadone Maintenance Therapy population.
- *St. James’s Hospital, Annual Multi – Disciplinary Research, Clinical Audit & Quality Improvement Seminar, May 2015, Poster Presentation.* Coghlan M, Bannan C, Broderick M, Murray C, Bergin C. Interferon Free Hepatitis C Treatments: Experience to date in the co-infection setting.

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Appendices

Appendix 1: Medication reconciliation study. Research ethics approval letter

THIS NOTE/PAPER MUST NOT BE USED FOR
PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie



**THE ADELAIDE & MEATH
HOSPITAL, DUBLIN**
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Miriam Coghlan
Hepatitis C Pharmacist
St. James's Hospital
James's Street
Dublin 8

9th May 2016

Re: Protocol Study 2: What are the processes and resources involved in gathering and maintaining an accurate patient medication record for patients receiving Hepatitis C therapy in an outpatient setting?

REC Reference: 2016 - 05 Chairman's action (11)
(Please quote reference on all correspondence)

Dear Ms. Coghlan,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you requested ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this correspondence and deems it an audit and therefore there are no ethical issues with proceeding.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 2: Drug-drug interaction study. Research ethics approval letter

THIS NEWSPAPER MUST NOT BE USED FOR
PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie



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Ms. Miriam Coghlan
Hepatitis C Pharmacist
St. James's Hospital
James's Street
Dublin 8

9th May 2016

Re: Protocol Study 3: Prevalence, clinical significance, management and outcome of drug-drug interactions between DAA based Hepatitis C treatment regimens and concomitant medicines in patients attending the outpatient department in a large Irish teaching hospital.

REC Reference: 2016 - 05 Chairman's action (12)
(Please quote reference on all correspondence)

Dear Ms. Coghlan,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you requested ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this correspondence and deems it an audit and therefore there are no ethical issues with proceeding.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human

Appendix 3: Medication reconciliation study: Data collection form

Assigned Patient Study Number & Initials		No. of concomitant medicines (pre-medication reconciliation)		No. of concomitant medicines (post-medication reconciliation)							
Gender	M / F	Age	Allergy status documented	Y / N	Outpatient clinic	ID/Hepatology					
Allergies	Liver cirrhosis		Y/N		No. of medication reconciliation issues for this patient						
Co-morbidities											
Sources of Medication Reconciliation used		Community pharmacy <input type="checkbox"/>	Patient relative <input type="checkbox"/>	No. of sources used for Medication Reconciliation							
		GP <input type="checkbox"/>	Patient medical notes <input type="checkbox"/>								
		Patient <input type="checkbox"/>	Electronic patient record <input type="checkbox"/>								
		Patient list <input type="checkbox"/>									
		Other: _____									
Resources used to complete medication reconciliation process			Phone	Paper records	Face to face						
			Email	Electronic records							
Treatment start date		Treatment finish date		SVR 12 Achieved							
Patient Medication											
Date	Drug Name	Dose	Freq	Route	Form	BNF Class	Documented in medical notes	Not documented	Dose Variance	Frequency Variance	Other medication variance

Medication variance unique number		Medication variance unique number		
Type of error	Error of omission <input type="checkbox"/> Error of commission <input type="checkbox"/> Undocumented <input type="checkbox"/> Dose Error <input type="checkbox"/>	Frequency error <input type="checkbox"/> Other <input type="checkbox"/>	Type of error Error of omission <input type="checkbox"/> Error of commission <input type="checkbox"/> Undocumented <input type="checkbox"/> Dose Error <input type="checkbox"/>	Frequency error <input type="checkbox"/> Other <input type="checkbox"/>
Follow up required			Follow up required	
Issue resolved			Issue resolved	
Reason for error			Reason for error	
Outcome			Outcome	

Appendix 4: Medication reconciliation assessment of variances: Medication variance assessment form

Assigned Patient Study Number		Gender		Age		Allergies					
Co-Morbidities	-										
Variances											
Variance 1											
	0	1	2	3	4	5	6	7	8	9	10
Variance 2											
	0	1	2	3	4	5	6	7	8	9	10

Appendix 5: User guide for the visual analogue scale in the medication variance study

Determining the potential severity of medication variances identified at the point of medication reconciliation, completed by hospital pharmacists in a Hepatitis C outpatient clinic

Instructions

Thank you for agreeing to participate in this study. Your role is to identify the **potential severity** of the **failure to reconcile medication** at each patient's outpatient appointment in a Hepatitis C clinic. At the time of the clinic review each patient was being assessed for suitability to start Hepatitis C treatment. A number of patient cases are presented below. For each case, the following information is provided:

1. The patient's demographic and clinical details.
2. Description of medication lists and the issue(s) identified.
3. The visual analogue scale for scoring, in your opinion, the potential harm to the patient consequent to the identified problem(s).

Please read through each case and indicate what you think is the potential for harm to the patient if the medication variance(s) between the medication history taken by the doctor and the medication reconciliation were not identified and rectified prior to the patient starting on Hepatitis C treatment with direct acting antivirals.

There are __ cases in this set and they should take approximately __ hours to complete.

The visual analogue scale for scoring the potential for harm¹. Please choose a score to reflect the potential harm that you consider could have been caused to this patient consequent to the identified variance(s).

Please score the potential harm that may have arisen to this patient consequent to the identified issue(s). (0=no harm, 10 = death).

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Once complete, please return in the stamped addressed envelope provided or by email to: Miriam Coghlan, Pharmacist, Pharmacy Department, Hospital 7, St. James's Hospital, Dublin 8. Email coghlanm@tcd.ie.

References:

¹Dean BS, Barber ND. Validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm 1999; 56: 57–62.(231)

²Grimes T. AMNCH Integrated Medication Management Study Tool (232)

Appendix 6: Standardised drug-drug interaction reference list

Resource and Accessibility	Guidance on use and important information
Hepatitis C Specific Resources	
<p>University of Liverpool Hepatitis C Drug Interaction Charts www.hep-druginteractions.org</p>	<ul style="list-style-type: none"> • Select the patient’s treatment regimen • Select the patient’s concomitant medicines • Note: not all medicines are listed for searching. • Not all medication interactions have been studied. Some results report the expected interaction based on pharmacokinetic data of the individual medicines rather than completed interaction studies.
General resources	
<p>Summary of Product Characteristics Irish licensed products via www.medicines.ie www.hpra.ie Unlicensed products FDA approved drugs should have a SPC available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. The SPC is under ‘Label Information’ and the most recent revision should be chosen</p>	<ul style="list-style-type: none"> • Document the source of the SPC, the full title and the date last updated. • Look at Section 5.2 - Pharmacokinetic information <ul style="list-style-type: none"> ▪ Metabolic route (renal, hepatic etc.) ▪ Any cytochrome P450 enzymes involved ▪ Any other relevant pharmacokinetic information • Look at Section 4.5 – Interaction with other medicinal products and other forms of interactions <ul style="list-style-type: none"> ▪ Any interactions with medications on the patient’s medication list. ▪ Any information on induction or inhibition of cytochrome P450 enzymes ▪ Note- Interactions listed can be theoretical; manufacturer may clarify. • Look at Section 4.4 – Special warnings and precautions for use <ul style="list-style-type: none"> ○ Search in particular for any reference to QTc prolongation • For pharmacodynamics interactions take note of the most common adverse reactions and cautions for comparison with other medication
<p>British National Formulary</p>	<ul style="list-style-type: none"> • In the electronic BNF, type the drug name in the search box, on the results page click the ‘interactions’ tab. • Look up interaction section for the medicine • Check for interactions with patients’ medications and document along with severity of interaction • In the online version

	<p>Interactions shown in bold and against a pink background are potentially serious; concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring). Interactions that are not in bold type do not usually have serious consequences.</p> <ul style="list-style-type: none"> • In the book version <p>Interactions with a black dot are potentially serious</p> <p>Interactions that have no symbol do not usually have serious consequences</p> <ul style="list-style-type: none"> • Consider significance for your patient even if the BNF doesn't rate the significance highly.
<p>Martindale Hard copy via www.medicinescomplete.com</p>	<ul style="list-style-type: none"> • Document monograph used and date of last modification • Check Interactions section of monograph for relevant information and management
<p>Stockley's Drug Interactions Hard copy or via www.medicinescomplete.com</p>	<ul style="list-style-type: none"> • Search using two drugs at a time • Results divided into specific and general • Note in particular 'Importance and Management' section • References provided if necessary
<p>Micromedex (Drug Reax) via www.tcd.ie/library</p>	<ul style="list-style-type: none"> • Use Drug Reax Interaction checker tool tab in top left corner • Onset time is given <ul style="list-style-type: none"> - Rapid – up to 24 hours - Delayed – after 24 hours • Check severity of interaction, defined as <ul style="list-style-type: none"> - Contraindicated – drugs are contraindicated for concurrent use - Major – the interaction may be life threatening and/or require medical intervention to minimise or prevent serious adverse events - Moderate – the interaction may result in an exacerbation of the patient's condition and/or require modification of therapy - Minor – the interaction would have limited clinical effects. Manifestations include an increase in the frequency or severity of side effects but generally would not require a major modification in therapy. - Unknown – the level of severity is not defined.
Second line resources	
Lexi –Interact	<ul style="list-style-type: none"> • Multi – Drug interaction checker – add in all patients' medication and press search.

	<ul style="list-style-type: none"> • Check risk rating for each interaction identified. Each letter designation (A, B, C, D, X) represents the severity level of the identified interaction. (X = Most severe) • Full details on the interactions with suggested management can be found by clicking on the interacting drug name. • Also note the onset time of the interaction. Onset time is defined as <ul style="list-style-type: none"> - Immediate – up to 12 hours - Rapid – from 12 hours to 72 hours - Delayed – More than 72 hours • The severity of the interaction is also important. Severity is defined as <ul style="list-style-type: none"> - Major - Effects may result in death, hospitalisation, permanent injury or therapeutic failure - Moderate – Medical intervention needed to treat effects but effects do not meet criteria for major - Minor – effects would be considered tolerable in most cases: no need for medical intervention
<p>Medscape (Drug Information Facts) via www.medscape.com</p>	<ul style="list-style-type: none"> • Multi-drug interaction checker – type in all patient’s medication and search • Take note of the severity of the interactions found. All interactions classified by severity <ul style="list-style-type: none"> - Contraindicated – This drug combination is contraindicated and generally should not be dispensed or administered to a patient - Severe – Action is required to reduce the risk of severe adverse interaction - Moderate – Assess the risk to the patient and take action as needed • Note Medscape does not provide references to double check information.
<p>Drugs .com</p>	<ul style="list-style-type: none"> • No sign in required • Interactions divided into professional and consumer data – use professional data • Three levels of significance <ul style="list-style-type: none"> - Major: Highly clinically significant; the risk of the interaction outweighs the benefit - Moderate: Moderately clinically significant. Usually avoid combinations; use it only under special circumstances - Minor: Minimally clinically significant. Minimise risk; assess risk and consider an alternative drug. Take steps to circumvent the interaction risk and/or institute a monitoring plan.
<p>Cytochrome p450 website: http://medicine.iupui.edu/flockhart</p>	<ul style="list-style-type: none"> • Indiana university website. • A table containing drugs listed in columns under specific cytochrome P450 isoforms. Drugs are included if

<p>∟</p>	<p>there is published evidence that they are metabolised, at least in part, via the specific CYP isoform.</p> <ul style="list-style-type: none"> • Useful if other medications on patients list are metabolised by CYP450
<p>CYP enzymes, substrates and inhibitors via http://www.pharmacologyweekly.com/content/pages/drug-reference-table-cyp-p450-ugt-enzymes-transporters-ab</p>	<ul style="list-style-type: none"> • CYP enzymes substrates/ inducers/ inhibitors and p-gp substrates are listed alphabetically by drug name. • Useful to quickly check metabolic pathways of drugs • Not all cytotoxic drugs available
<p>Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes (TdP) www.azcert.org</p>	<ul style="list-style-type: none"> • A list of drugs that prolong QT interval and/or induce TdP drugs are categorised into those that: <ul style="list-style-type: none"> - are considered to carry a risk of TdP. - prolong QT interval and/or have been associated with TdP, but at this time lack substantial evidence for causing TdP. - carry a risk of TdP and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs. • Useful to quickly check if medications prolong QTc

Appendix 7: Drug-drug interaction study data collection form

Patient initials and study number:				
MRN:			Gender: M / F	
Outpatient clinic: Hepatology <input type="checkbox"/> <input type="checkbox"/>				
Cirrhotic: Yes <input type="checkbox"/> No <input type="checkbox"/>			Genotype:	
Treatment regimen:			Treatment start date:	
			Treatment finish date:	
Treatment Duration:			Treatment outcome:	
Concomitant medication	Dose & Frequency	Interaction potential	Action Taken	Monitoring Plan

Appendix 8: Complementary and alternative medicines. Research ethics approval

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email: claire.hartin@amnch.ie

Ms. Miriam Coghlan
Senior Hepatitis C Pharmacist
St. James's Hospital
James's Street
Dublin 8

31st May 2017

Re: An Assessment of patient knowledge and attitudes towards complementary and alternative medicines (CAM) among a Hepatitis C Seropositive population

Reference: 2017-05 Chairman's Action (22)
(Please quote reference on all correspondence)

Dear Ms. Coghlan,

The REC is in receipt of your recent application to SJH/AMNCH Research Ethics Committee in which you queried ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your application and granted ethical approval for this study.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Ms Miriam Coughlan,
St James's Hospital,
James' Street,
Dublin 8

17th April 2019

Re: An assessment of patient knowledge and attitudes towards CAM among HCV seropositive populations

REC Reference: 2019-04 List 13 (15)
Previous REC Reference: 2017-05 Chairman's Action (22)
(Please quote reference on all correspondence)

EudraCT Number:

Date of Valid Submission to REC: 14.03.2019
Date of Ethical Review: 12.04.2019
R&I application Number: N/A

Dear Dr Coughlan,

Thank you for your correspondence in which you submitted an amendment for the above named study.

The Chairman has reviewed the documentation you submitted and has given approval for this study to proceed. The following comments were made:

- Please add the co-investigators details to the PIL
- Please remove the controller email as this is the DPO email
- Please add section 'why me?'

The following documents were reviewed:

- Non-clinical amendment form, dated 13.03.2019
- PIL
- CF

Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.

Yours sincerely,



REC Officer – Dr Sadhbh O'Neill - SJH/TUH Research Ethics Committee

Appendix 9: Complementary and alternative medicines survey

Section 1. Background information

1. Age (in years) or dob: _____

2. Initials: _____

3. What is your country of birth? _____

4. What is the highest level of education you have completed?

Primary school

Secondary school

Third level

5. What is your current employment status?

Full-time employment

Part-time

House-duties

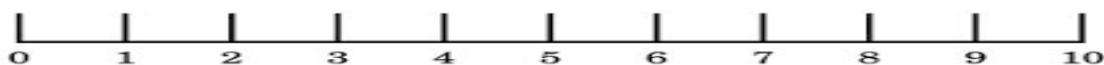
Retired

Student

Unemployed

Asylum-seeker

6. On a scale from 0-10, how would you rate your quality of life? (where 0 is the lowest quality and 10 is the highest quality)



7. In general would you consider your health:

Excellent

Very good

Good

Fair

Poor

8. Is your daily activity or work limited by a long-term illness, health problem or disability?

Yes,

No

Not applicable

If so, in what way?

9. Have you ever been hospitalised for management of a liver-related condition?

Yes

No

Uncertain

Not applicable

If so for what:

Complementary and Alternative Medicines (CAM) is the term for medical products and practices that are not part of standard medical care that can include herbs, supplements, vitamins, protein shakes and other nutritional products.

10. Have you ever used a complementary or alternative medicine?

Yes No* Uncertain*

(If your answer to this question is No or Uncertain please move to section 3)

Section 2. Use of Complementary and Alternative Medicines

11. Have you used or are you currently using any of the following complementary or alternative medicines? (Interviewer to have a sheet with examples of each of these with names and photos)

Herbal Medicines

Herbal teas or tinctures

Homeopathic remedies

Vitamin & mineral supplements

Gym/ workout / bodybuilding supplements

Other (please specify):

12. For the CAM product(s) you are currently using, are you using it to treat a medical condition? If yes, please describe.

13. For the CAM product(s) you are currently using, how long are you using it/them for?

14. For the CAM product(s) you are currently using, why did you start using them?

15. Where did you hear of or learn about the CAM product(s) you are using?

From a friend
From a family member
From ads on the TV/radio/newspapers/magazines
From the Internet
Recommendation from a CAM practitioner
From a Healthcare provider
In a health food shop

Other: _____

16. Do you generally use CAM:

In addition to prescription medications

Instead of prescription medications

Other (please specify): _____

17. Do you always remember to tell your doctor and your pharmacist that you are taking CAM?

Yes No Sometimes

18. From where do you generally purchase CAM products? (more than one option can be selected)

CAM practitioner

Gym

Health food shop

Supermarket

Online Supermarket

Pharmacy

Other (please specify): _____

19. In the past 12 months, about how much money have you spent on buying CAM products?

A CAM practitioner can be described as person who advises on the use of CAM products.

20. Have you ever consulted with or seen one of the following CAM practitioners?

Acupuncturist

Chinese practitioner

Chiropractor Herbalist

Homeopath

Massage therapist

Naturopath

Other (please specify): _____

21. In the past 12 months, have you consulted a CAM practitioner about CAM?

Yes No Uncertain

22. If yes, how many times have you consulted a CAM practitioner in the past year?

23. In the past year, about how much money have you spent attending CAM practitioners?

24. When you purchase CAM products are you asked by the CAM provider about other medications or health conditions that you might have?

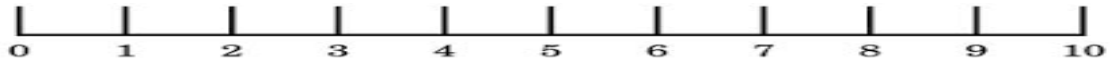
Yes, always

Yes, sometimes

Never

Uncertain

25. Are you generally satisfied with your CAM therapies? (where 0 is not happy at all and 10 is very satisfied)



26. Do you feel CAM therapies have made your overall health:

Much better

Better

Made no difference

Worse

Much worse

Can you tell me a bit more? _____

27. Are there CAM products that you have used in the past but no longer use? Is so, what and why? E.g. have you ever had side-effects from CAM products?

Section 3. Participants who have not previously used CAM products

Have you ever considered using CAM?

Yes

No

Maybe

Has CAM ever been recommended to you?

Yes

No

Not sure

If yes, by whom? _____

Do you consider yourself knowledgeable about CAM?

Yes

No

Uncertain

Please explain why you do not use CAM or would not consider using CAM.

Thank you for taking part in this survey, your help is much appreciated.

Appendix 10: Complementary and alternative medicines study patient information leaflet and consent form.



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Patient Information Leaflet and Consent Form
An assessment of patient knowledge and attitudes towards
complementary and alternative medicines (CAM).
Hepatology Clinic, St. James's Hospital

Principal investigator's name: Ms. Miriam Coghlan

Principal investigator's title: Senior Clinical Pharmacist

Telephone number of principal investigator: 01-4162037

Co-investigators: Prof. Colm Bergin, Consultant Physician, St. James's Hospital

Prof. Suzanne Norris, Consultant Physician, St. James's Hospital

Dr. Aisling O'Leary, Chief II Pharmacist, National Centre for Pharmacoeconomics

Data Controller's Identity: St. James's Hospital

Data Controller's Contact Details: dataprotection@stjames.ie

Data Protection Officer's Identity: Data Protection Officer

Data Protection Officer's Contact Details: dataprotection@stjames.ie

You are being invited to take part in a research study to be carried out at St. James's Hospital by Trinity College.

Before you decide whether or not to take part in this research study, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – don't feel rushed and don't feel under pressure to make a quick decision. It is important that you understand why the study is being done, the possible risks and benefits of the study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

Please read this information carefully and if you have further questions, please ask a member of the study team.

You don't have to take part in this study. If you decide not to take part it won't affect your future medical care. You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You don't have to give us a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

Why is this study being done?

The objective of this study is to assess the level of knowledge about, and use of, complementary and alternative therapies (CAM), in Ireland.

The use of complementary and alternative medicines (CAM) among patients has become more common. However, it is known that the use of multiple medications, herbs or nutritional supplements are not without the potential to cause adverse effects for patients. This study aims to provide a better understanding of patient motivations for use of complementary and alternative medicines and also to better describe the types of CAM products in use.

The Study Design

This study is being completed as part of a PhD research project in conjunction with the School of Medicine, Trinity College. No funding has been received to help completion of this research.

A total of approximately 50 patients will participate at St. James's Hospital.

You are being asked to take part because you attend the Hepatology Department at St. James's Hospital.

If you are eligible to enter the study, you will be asked to complete a questionnaire relating to knowledge and use of CAM products. You will be brought to a clinic room within the Hepatology

department to complete the questionnaire in private. You will also be asked questions about your lifestyle, general health and wellbeing as part of the questionnaire. The questions about you are asked because the use of complementary and alternative medicines has been shown to be linked with social factors and it is important that we capture this information. This questionnaire should take approximately 15 minutes to complete. A study team member will be available to answer any questions you might have about the questionnaire. In addition to completion of the questionnaire, a member of the study team will also review your medical notes to gather information relating to co-morbidities, especially liver health and medications in use. Information from your medical records will be kept private and pseudonymised during the research process.

Clinic Visits and Procedures

No additional clinic visits are required to participate in this study.

If, after reading this information sheet, you decide to take part you will be asked to sign this form confirming that you agree to participate. Please hand it back to the doctor, nurse or pharmacist who sees you.

Risks of Participating in the Study

There are no risks to participating in this study.

Benefits of Participating in the Study

The information gained from this study may be of benefit in providing advice and information to patients on the safe use of complementary and alternative medicines. It may be used to guide decision makers on the importance of identifying CAM use among the patient population. However, we cannot guarantee that you as an individual will receive any benefits from this study. Only you can decide whether to join the study. This involves giving written consent. Please ask your clinic doctor or nurse questions about the trial. If you do not participate, it will not affect your future medical care.

Is the study confidential?

We will not be contacting your GP or other healthcare providers as part of this study. Your medical records will be accessed by the principal investigator only. Information about you will be kept private and confidential. Your information will be anonymised and therefore will not identify you. Information collected as part of this study will be retained for five years after completion of this study. Only the principal investigator and data controller will be able to see the study information gathered from you.

Will I be told the outcome of the study?

You will not receive any results from this research project however the study results will be of benefit in the provision of advice and information to patients on the safe use of complementary

and alternative medicines in the future. The results of this study will be published in medical journals and may be presented at medical conferences however no information that will identify you as a participant will be presented.

8. Data Protection

- We will be using your personal information in our research to help us to better understand patient motivations for use of complementary and alternative medicines and also to better describe the types of CAM products in use.
- The lawful basis for processing this study data comes from General Data Protection Regulations 2018:
 - Article 6; 1 a) The data subject has given consent to the processing of his or her personal data for one or more specific purposes.
 - Article 6; 1 e) processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller.
 - Article 9;2(j): processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1) based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject.
- Only the principal investigator and data controller will be able to see the study information gathered from you.
- Information about you that is collected as part of this study will be retained for five years after completion of this study.
- Data collected as part of this study will be held as anonymised data on a restricted access and password protected computer server at St. James's Hospital to minimise the risk of a data breach. If a data breach does occur the Data Protection Commissioner and the patients affected will be contact within 72 hours.
- Your participation in this study is entirely voluntary. If you decide not to take part or to withdraw from the study at any time, you will not be penalised nor lose any benefits to which you are otherwise entitled. To withdraw consent please contact the principal investigator.
- If you wish to lodge a complaint in relation to the study you may do so at any time. The details of how to make a complaint are provided further down in the information leaflet.

- You have the right to request access, and obtain a copy of, to your personal data gathered as part of this study.
- You have the right to restrict or object to processing of your data, unless your request would make it impossible or make it very difficult to conduct the research.
- You have the right to have any inaccurate information about you corrected or deleted, unless your request would make it impossible or make it very difficult to conduct the research.
- You have the right to have your personal data collected during this study deleted, unless this request would make it impossible or make it very difficult to conduct the research.
- You have the right to transfer your data to another data controller if requested.
- There will be no automated decision making or profiling completed as part of this research study.
- You will be informed if the study team intend to further process your personal data and you will be provided with information on that other purpose.
- You will be informed if the study team wish to transfer your data to a country outside of the EU or an international organisation and you will be advised of the safeguards that are in place to protect their data.

9. Questions about the study/Further information

If you have any further questions about the study or if you want to opt out of the study, you can rest assured it won't affect the quality of treatment you get in the future.

If you need any further information now or at any time in the future, please contact:

Name: Miriam Coghlan

Address: Pharmacy Department, St. James's Hospital, Dublin 8

Phone No: 01 4162037

10. Statement of Subject Rights

The study team will have explained the details of this study to you and answered any questions you may have. You should be satisfied with the information you have been given and had adequate time to consider whether you want to participate. If you decide you would like to take part in this

study, you will be asked to sign a consent form. If you do not want to take part, or if you choose to withdraw from the study at any time, you will continue to receive the best medical care offered by your doctor.

All information obtained in connection with this study will remain confidential. You will be identified by your initials and a subject number (assigned to you as part of the study) on data collection forms. You will not be identified in any publication or public presentation of data from this study. Only authorised personnel from the hospital outpatient service, the researchers and government regulatory authorities will have access to your medical records. By signing this form, you give permission that these authorised persons may access your medical records. However, your records will always be treated as strictly confidential.

11. Has this study been reviewed by an Ethics Committee?

This study has been reviewed the Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee (REC).

CONSENT FORM

I consent to participate in the study described in the patient information statement set out in the attached form.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I acknowledge that I have read and understood the patient information leaflet, which explains why I have been selected, the aims of the experiment and the nature and the possible risks, benefits and alternatives of this study, and the information has been explained to me to my satisfaction.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I understand that I don't have to take part in this study and I can withdraw from the study at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I give permission for researchers to look at my medical records to get information. I have been assured that information about me will be kept private and confidential.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I give informed explicit consent to have my data processed as part of this research study.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I understand that if I have any questions relating to my participation in this research, I may contact Ms Miriam Coghlan (01-4162037).	YES <input type="checkbox"/>	NO <input type="checkbox"/>
I consent to be contacted by researchers as part of this research study.	YES <input type="checkbox"/>	NO <input type="checkbox"/>

I have been given a copy of the Information Leaflet and this completed consent form for my records.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
---	------------------------------	-----------------------------

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
--	------------------------------	-----------------------------

I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
--	------------------------------	-----------------------------

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

Appendix 11: Epilepsy study. Research ethics approval

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PRESCRIPTIONS OR INVOICING PURPOSES



40117

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

**THE ADELAIDE & MEATH
HOSPITAL, DUBLIN**
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Waiver of Ethical Approval

01 December 2017

Re: "Audit"

Dear Miriam,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you enquired about ethical approval for your proposed Audit/Service Improvement.

The SJH/AMNCH do not ordinarily concern themselves with audits or service improvements that do not involve direct patient contact and therefore there are no ethical issues with proceeding.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.



Participant Information

Feasibility & Acceptability of a Hepatitis C pre-treatment assessment complex intervention tool

Pharmacy Department, St. James's Hospital.

You are invited to participate in the research study outlined below.

1. Background to Research Study

Before you decide whether or not to take part in this research study, it is important that you understand why the study is being done. Please read this information carefully and if you have further questions, please ask a member of the study team.

2. Purpose of the Study

The objective of this study is to assess the feasibility and acceptability of a Hepatitis C pre-treatment complex assessment complex intervention tool.

3. The Study Design

A total of 30 healthcare professionals will participate in this study which is based at St. James's Hospital. As part of this study you will be asked to complete an interview relating to your role in Hepatitis C patient care and your knowledge and use of complex intervention tools in everyday healthcare practice. This should take approximately 30-45 minutes to complete. A study team member will complete the interview and will answer any questions you might have about the complex intervention tool or the study design. The interview sessions will be recorded to aid the capture of all relevant information from each interview session in a timely manner. The interviewer will also take written notes. If you are not happy to have the interview session recorded please let the interviewer know.

4. Risks of Participating in the Study

There are no risks to participating in this study.

5. Benefits of Participating in the Study

The information gained from this study will allow formal assessment of the feasibility and acceptability of this Hepatitis C pre-treatment assessment tool as an aid to optimal treatment selection. However, we cannot guarantee that you as an individual will receive any benefits from this study. Only you can decide whether to participate in this study.

7. Questions about the study

If you have any questions about the study, please contact the primary investigator at coghlam@tcd.ie.

8. Statement of Subject Rights

Your participation in this study is entirely voluntary. You may decide not to take part or to withdraw from the study at any time.

All information obtained in connection with this interview will remain anonymous. You will be identified by your subject number (assigned to you as part of the study) on data collection forms. You will not be identified in any publication or public presentation of data from this study. Only authorised personnel from the researcher team will have access to the study data.

9. Who is organising and funding this research?

This research is being funded a pharmacist research bursary from the Irish Hepatitis C Research and Outcomes Network (ICORN).

10. Has this study been reviewed by an Ethics Committee?

This study has been reviewed the Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee (REC).

Participant Name: _____

Study interviewer name: _____

Date: _____

Appendix 13: Complex Intervention Toolkit Feasibility Study: Topic guide

Introduction and opening

_____ I would like to start by saying thank you very much for agreeing to participate in this feasibility study interview for the Hepatitis C pre-treatment pharmacist assessment complex intervention toolkit.

To give you a brief outline of how this session will run. It will be approx. 30-45 mins in length. I will initially ask you some specific questions around your experience working with patients with Hepatitis C and the specific roles you complete as part of their care. The session will also aim to

gain your opinion and insight on the changes currently underway within the Hepatitis C care model in Ireland.

The session will then progress to focus specifically on the Hepatitis C pre-treatment pharmacist assessment complex intervention toolkit. I will provide you with a copy of the toolkit and we will review this throughout the session to gain your opinions and feedback on various aspects of its structure, content and user friendliness.

I am very grateful for your time today to complete this valuable process as I am to create a useful resource for healthcare professionals who are involved in HCV care across all healthcare settings.

Questions: For HCPs who are already involved in the care of HCV patients

Introductory

1. What is/are your role(s) in the healthcare team?
2. Are you involved in the care of patients with Hepatitis C?
3. How many days per week (on average) do you care for/see patients in relation to management of their HCV infection?
4. In what healthcare setting(s) do you provide care for patients with HCV?
5. How long have you been involved in caring for patients with HCV?
6. What is/are your role(s) in the care of patients with HCV?
7. If you had to rate your knowledge of HCV as a condition and its treatment out of 10, with 0 being no knowledge, what score would you give and why?
8. What part of HCV patient care do you find you have least knowledge about?
9. What part of HCV patient care do you find most challenging?
10. What in your opinion are the service provision factors which may impact the success of HCV DAA therapy for an individual patient?
11. What in your opinion are the most important patient clinical factors which must be considered by the healthcare team when choosing the optimum HCV treatment regimen for a patient?
12. In relation to your answers for the last two questions do you think the current model of care provides you with the ability/tools/resources to choose the optimum regimen and provide a service which gives a patient the best chance of SVR?
13. Do you think the current model of care as it expands?

Complex intervention toolkits can facilitate healthcare professionals in making clinical decisions related to patient management. E.g. STOPP/START.

14. Do you currently use any specific intervention tools or toolkits in your everyday work?
15. Do you perceive the intervention toolkits are beneficial in the healthcare setting?
16. Do you think an intervention toolkit to guide optimum treatment of HCV patients would be beneficial to you in your everyday practice?

We will now review the PTPA CIT together and I will provide explanations for the content and intended use of the CIT sections and associated training guides. Please feel free to ask questions as I explain the CIT. There will also be some specific questions are the review.

17. What are your first impressions of the PTPA CIT?
18. Is this something you would consider using in your role in HCV patient care?
19. What part do you like best?
20. What part do you like least?
21. Are there any sections you think are unnecessary or that you would remove?
22. What is your opinion of the associated training guides?
23. Do you think this PTPA CIT would be a beneficial addition to the HCV treatment model in Ireland?
24. Where do you think the PTPA CIT would sit best within the HCV treatment model?
25. Are there particular HCP staff groups that you think would benefit more from the PTPA CIT than others and if yes how so?
26. Do you think use of the PTPA CIT would change your assessment of HCV patients for treatment in any way?
27. Do you think the PTPA CIT would increase the number of patients you review for HCV treatment assessment?
28. Would you like to see the PTPA CIT or something similar incorporated into the NHCTP as a HCP resource?

Open session for any questions or comments from the interviewee

Closing

Summarise general themes of the discussion and insight that came out of the conversation and give participants an opportunity for any final words, thank them for their input, inform them how the data will be used and explain how the results will be disseminated.

Appendix 14: Complex Intervention Toolkit Feasibility Study: Research Ethics Approval

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39/17

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

**THE ADELAIDE & MEATH
HOSPITAL, DUBLIN**
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Waiver of Ethical Approval

30 November 2017

Re: "Peer-to-Peer Research"

Dear Miriam,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you enquired about ethical approval for your proposed research/amendment.

The SJH/AMNCH do not ordinarily concern themselves with peer-to-peer research, audits or service improvements that do not involve direct patient contact and therefore there are no ethical issues with proceeding.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 15: Complex intervention toolkit pilot and evaluation study: Toolkit format

Hepatitis C Pharmaceutical Care Process Complex Intervention Toolkit

Step 1: Patient baseline characteristics

Patient Age	yrs	Gender	
Patient Weight	kg	Date of weight	
Hepatitis C Genotype		HCV Viral Load	Date:
First Diagnosed		Route of acquisition	
Liver Disease Staging	Fibroscan: _____ kPa Date:	Biopsy: _____ Date:	Ultrasound/CT: _____ Date:
Co-morbidities			
Alcohol Intake			
Allergy Status			
Baseline Laboratory Markers	AST	ALT	Bilirubin
	Na ⁺	Platelets	Creatinine
Date of Labs:	Albumin	Gamma GT	Alpha-feto protein
	INR	Dialysis	Y/N
Renal Function	Cockcroft & Gault		Date
Hepatitis B Markers	Core Antibody		Surface Antibody
	Surface Antigen		HBV viral load
	Hepatitis B e Antigen (If HBV infection confirmed)		e Antigen positive
HIV Ag/Ab Combo			
Based on the available information does this patient have cirrhosis? If yes, please complete below questions		Yes	No
If cirrhotic, has this patient had an episode(s) of hepatic decompensation?		Yes	No
Ascites	Yes / No	Encephalopathy	Yes / No
Varices	Yes / No	Portal HTN	Yes / No

Hepatic Function Measurement in patients with liver cirrhosis	Child Pugh Score	MELD Score	FIB-4 Score
Date:			

Step 2: Medication Reconciliation

When obtaining information relating to medication taken by a patient please ensure information on all potential medication forms is obtained. (Oral medications, topical agents, transdermal patches, inhalers, eye drops, herbal teas etc.)

Information sources used to determine the patient's current medications:

Patient interview		Contact with Community Pharmacy		Patient hospital medical notes	
Patient's own medication list		Contact with Drug Treatment Centre		Electronic patient records	
Patient's own medications		Contact with GP		Other healthcare providers	
Contact with a patient carer/relative					

Source	Medication List	Potential for DDI
Community pharmacy		
Drug treatment clinic		
Hospital Outpatient Clinic		
Health food Shop /Supermarket/Gym supplements		
Online		
Illicit		

Other		
Contraception planning for both patient and partner(s) while on Hepatitis C treatment.		

Step 3: Review of the proposed HCV treatment regimen

HCV Genotype		HCV VL		Date	
HCV Treatment History	Treatment naïve		Treatment experienced		
Previous treatment regimens					
Previous Treatment response	Relapse	Partial response to IFN/RBV	Null responder	Viral breakthrough on treatment	
If treatment experienced with DAAs please document resistance profile					
Proposed treatment regimen					
Is ribavirin co-prescribed?	Yes		No		
Proposed treatment duration	8 weeks		12 weeks		
	24 weeks		Other:		
Does the proposed treatment regimen meet National treatment guidelines?	Yes		No		

Step 4: Drug-drug interaction review (See reference resource list)

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan

Outcomes of MDT report discussion and plan:

PTPA toolkit completed by: _____ Date: _____

Appendix 16: Complex intervention toolkit pilot and evaluation study: Data collection form for Group B participants completing test cases using standard of care.

Case Number	Case decisions/Answers
1	
2	
3	
4	
5	
6	
7	
8	

Appendix 17: Complex Intervention Toolkit Evaluation Study: Patient test cases

Case 1

Male, 52 years old

Risk of Hepatitis C acquisition: Injecting drug use

Co-morbidities: HIV co-infection, Hepatitis B core antibody positive, thrombocytopenia, bipolar disorder, addiction, osteoporosis, previous pulmonary TB infection.

NKDA

Co-medications:

- Tenofovir 245mg once daily
- Raltegravir 400mg BD
- Atazanavir/ritonavir 300mg/100mg once daily
- Co-trimoxazole 960mg once daily
- Solpadeine: 2 tablets TDS as required
- Vimovo® 500mg/20mg BD
- Lansoprazole 30mg once daily
- Denosumab 60mg twice yearly
- Calcichew D3 Forte®

Hepatitis C Genotype 1a, fibroscan 6.7kPa

Treatment naïve

Weight: 63.4kg

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	14.9g/dL	Sodium	137
Platelets	229	Albumin	48
INR	0.9	AST	41
Creatinine	119	ALT	53
Alpha-fetoprotein	2.1	Bilirubin	23

The consultant has provided you with a prescription for Viekirax®/Exviera® for 12 weeks. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this prescription provided by the consultant.

- Confirm if this is an appropriate regimen for this patient.
- Identify any discrepancies with the prescription if found.
- Please identify any relevant drug-drug interactions and appropriate management plans.
- Please comment on any other patient issues you identify as part of prescription screening and medication review.

Case 2

Female, 54 years, African origin

Risk of Hepatitis C acquisition: Heterosexual

Co-morbidities: HIV, gallstones, osteoporosis, Hepatitis B core antigen positive

Co-medications:

- Tenofovir 245mg once daily
- Emtricitabine 200mg once daily
- Raltegravir 400mg BD
- Antacids
- Aspirin 300mg PRN for analgesia

Hepatitis C G1a, Liver fibrosis staging: Fibroscan = 10.6kPa, and diagnosed as cirrhotic on imaging
Compensated cirrhosis (no history of ascites or encephalopathy)

Viral relapse after prior HCV treatment with interferon and ribavirin

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	13.7g/dL	Sodium	143
Platelets	330	Albumin	41
INR	0.9	AST	49
Creatinine	69	ALT	55
Alpha-fetoprotein	2.4	Bilirubin	5

The consultant has asked you what regimen would be appropriate to use for this patient. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this patient and answer the following questions.

- Please provide details of the Hepatitis C regimen you would recommend to the consultant for this patient.
- Please identify any relevant drug-drug interactions and appropriate management plans based on the regimen that you recommend.
- Please comment on any other patient issues you identify as part of this medication review.

Cas

e 3

Male, 51 years

Risk of Hepatitis C acquisition: MSM

Co-morbidities: Depression and anxiety, hayfever, chronic back pain and a history of alcohol excess

Co-medications:

- Sertraline 100mg mane
- Zolpidem 10mg nocte
- Alprazolam 250mcg BD/PRN
- Ixprim®: 2 tablets TDS/PRN
- Cetirizine 10mg once daily
- Fluticasone nasal spray

Hepatitis C Genotype 3, treatment naïve, fibroscan = 18kPa, compensated cirrhosis

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	15.0g/dL	Sodium	138
Platelets	185	Albumin	45
INR	1.0	AST	91
Creatinine	93	ALT	127
Alpha-fetoprotein	4.9	Bilirubin	10

The consultant has asked you what regimen would be appropriate to use for this patient. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this patient and answer the following questions.

- Please provide details of the Hepatitis C regimen you would recommend to the consultant for this patient.
- Please identify any relevant drug-drug interactions and appropriate management plans based on the regimen that you recommend.
- Please comment on any other patient issues you identify as part of this medication review.

Case 4

Male, 48 years

Risk of acquisition: Injecting drug use

Co-morbidities: Addiction, HIV, ulcerative colitis, depression.

Co-medications:

- Methadone 80mg once daily
- Mirtazapine 45mg nocte
- Mesalazine 1.6g TDS
- Pantoprazole 40mg once daily
- Hyoscine butylbromide 10mg TDS/PRN
- Tenofovir 245mg once daily
- Emtricitabine 200mg once daily
- Raltegravir 400mg BD

Hepatitis C Genotype 3, liver cirrhosis (fibroscan 13.4kPa), treatment naïve. No evidence of ascites or hepatic encephalopathy.

81.2kg

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	15.8g/dL	Sodium	142
Platelets	176	Albumin	40
INR	1.0	AST	30
Creatinine	70	ALT	35
Alpha-fetoprotein	5.3	Bilirubin	7

The consultant has prescribed sofosbuvir/daclatasvir and ribavirin for 24 weeks. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this prescription provided by the consultant.

- Confirm if this is an appropriate regimen for this patient.
- Identify any discrepancies with the prescription if found.
- Please identify any relevant drug-drug interactions and appropriate management plans.
- Please comment on any other patient issues you identify as part of prescription screening and medication review.

Case 5

Male, 46 years

Risk of acquisition: IDU

Co-morbidities: Addiction, asthma, history of excessive alcohol intake

Co-medications:

- Methadone 65mg once daily (via Drug Treatment Clinic)
- Diazepam 5mg TDS
- Flurazepam 60mg nocte
- Seretide Diskus® Inhaler 500mcg BD
- Salbutamol inhaler 100mcg QDS/PRN

Hepatitis C Genotype 3, treatment naïve

Liver cirrhosis present on ultrasound and fibroscan = 16kPa

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	14.0g/dL	Sodium	137
Platelets	88	Albumin	48

INR	1.0	AST	48
Creatinine	50	ALT	41
Alpha-fetoprotein	2.8	Bilirubin	15

The consultant has asked you what regimen would be appropriate to use for this patient. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this patient and answer the following questions.

- Please provide details of the Hepatitis C regimen you would recommend to the consultant for this patient.
- Please identify any relevant drug-drug interactions and appropriate management plans based on the regimen that you recommend.
- Please comment on any other patient issues you identify as part of this medication review.

Case 6

Male, 56 years

Risk of acquisition: IDU

Co-morbidities: Alcohol dependence syndrome, addiction, depression

Co-medications:

- Lansoprazole 30mg once daily
- Escitalopram 10mg once daily
- Zolpidem 5mg nocte

Hepatitis C Genotype 1a

Liver cirrhosis on fibroscan = 15.9kPa, no history of hepatic decompensation i.e. compensated cirrhosis

Prior treatment experience: Relapse post treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir and ribavirin x 12 weeks.

Resistance mutations identified at the timepoint of HCV treatment failure:

- Protease mutations: D168V, 174S
- NS5A mutations: Q30R

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	14.5g/dL	Sodium	141
Platelets	175	Albumin	47
INR	0.9	AST	57
Creatinine	67	ALT	62
Alpha-fetoprotein	45	Bilirubin	11

The consultant has asked you what regimen would be appropriate to use for this patient. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this patient and answer the following questions.

- Please provide details of the Hepatitis C regimen you would recommend to the consultant for this patient.
- Please identify any relevant drug-drug interactions and appropriate management plans based on the regimen that you recommend.

- Please comment on any other patient issues you identify as part of this medication review.

Case 7

Female 24 years old

Risk of acquisition: IDU

Co-morbidities: Depression and anxiety

Co-medications:

- Methadone 40mg once daily
- Sertraline 200mg once daily
- Diazepam 10mg TDS
- Zopiclone 15mg nocte
- Yasmin® combined oral contraceptive

Hepatitis C Genotype 1a, fibroscan = 6.8kPa, non-cirrhotic and treatment naïve.

59.6kg

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	13.8g/dL	Sodium	143
Platelets	146	Albumin	46
INR	1.0	AST	30
Creatinine	68	ALT	35
Alpha-fetoprotein	1.5	Bilirubin	5

The consultant has prescribed Viekirax/Exviera® and ribavirin 600mg BD for 12 weeks. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this prescription provided by the consultant.

- Confirm if this is an appropriate regimen for this patient.
- Identify any discrepancies with the prescription if found.
- Please identify any relevant drug-drug interactions and appropriate management plans.
- Please comment on any other patient issues you identify as part of prescription screening and medication review.

Case 8

Male 50 years

Risk of acquisition: IDU

Co-morbidities: Alcohol dependence syndrome, addiction, depression, portal hypertension, oesophageal varices

Co-medications:

- Methadone 60mg once daily
- Spironolactone 100mg BD
- Furosemide 40mg once daily
- Rifaximin 550mg BD
- Lactulose 20mls TDS
- Esomeprazole 40mg once daily
- Diazepam 5mg BD
- Temazepam 10mg nocte
- Thiamine 300mg once daily
- Mirtazapine 30mg nocte
- Propranolol 20mg BD

Hepatitis C G1a, with decompensated cirrhosis (ascites present), treatment naive

Laboratory Markers completed as part of this patient's pre-treatment assessment

Hb	12.3g/dL	Sodium	136
Platelets	78	Albumin	27
INR	1.4	AST	112
Creatinine	79	ALT	41
Alpha-fetoprotein	5.7	Bilirubin	36

The consultant has asked you what regimen would be appropriate to use for this patient. The above list of co-medication has been confirmed by medication reconciliation completed by one of your pharmacist colleagues.

Please review this patient and answer the following questions.

- Please provide details of the Hepatitis C regimen you would recommend to the consultant for this patient.
- Please identify any relevant drug-drug interactions and appropriate management plans based on the regimen that you recommend.
- Please comment on any other patient issues you identify as part of this medication review.

Appendix 18: Complex Intervention Toolkit Evaluation Study: Time to completion record form

Case Number	Total time to completion (mins)
1	
2	
3	
4	
5	
6	
7	
8	

Appendix 19: Complex Intervention Toolkit Evaluation Study: Training presentation

Hepatitis C Pre-Treatment Pharmacist Assessment Complex intervention tool Training Guide

Author: Ms. Miriam O'Leary
Senior Pharmacist, St. James's Hospital, Dublin
PhD Student, Trinity College Dublin




Step 1: Patient baseline characteristics

- Patient age
- Gender
- Weight
- Recent C. Coeotype: If ongoing risk behaviour consider checking HCV genotype every 12 months
- Recent C. coeotype: All patients must have a recent (last PCR result taken within the three months immediately prior to HCV treatment initiation)
- Liver Disease Staging*
 - Fibroscan
 - Ultrasound/USCT
 - Liver biopsy (if already completed)
 - ALT -> elevated
- Cirrhosis status

Step 1: Patient baseline characteristics

- Allergy status
- Baseline laboratory results
- Renal function
 - <https://www.nhs.uk/healthcareprofessionals/renal-conditions/renal-conditions/>
- Hepatitis B status: This is important in the context of the potential for Hepatitis B reactivation during therapy with HCV DAA.

Step 1: Patient baseline characteristics Liver Disease Staging: Fibroscan

Elastography (kPa)

Elastography of liver (kPa) - 0-150kPa (0-150kPa)

Step 1: Patient baseline characteristics Determination & Staging of Cirrhosis

Fibroscan score >12.5kPa considered as indicative of cirrhosis in non-alcoholics. Fibroscan score >15kPa considered as indicative of cirrhosis in alcoholics patients.

- <https://www.nhs.uk/healthcareprofessionals/renal-conditions/renal-conditions/>
- <https://www.nhs.uk/healthcareprofessionals/renal-conditions/renal-conditions/>
- <https://www.nhs.uk/healthcareprofessionals/renal-conditions/renal-conditions/>
- <https://www.nhs.uk/healthcareprofessionals/renal-conditions/renal-conditions/>
- Evidence of decompensation (ascites, encephalopathy, splenomegaly, variceal haemorrhage)
- History of hepatocellular carcinoma and treatment received
- If uncertainty, patient response to a combination regimen may also refer to Resolving and/or disease management at cirrhosis.

Step 2: Medication Reconciliation

1. Information sources used to determine the patient's current medications
 - Medication possession by general practice/hospital/health
 - How the number in a community pharmacy
 - Online
 - Social history
 - Appearances
 - Home visits
 - Relatives or friends
 - Other drugs
 - Homeopathic and/or proffered
 - Notes: E.g. Hospital and mental health including previous
2. Sources of medications
 - How the number in a community pharmacy
 - Online
 - Social history
 - Appearances
 - Home visits
 - Relatives or friends
 - Other drugs
 - Homeopathic and/or proffered
 - Notes: E.g. Hospital and mental health including previous

Medication Reconciliation

1. Obtain a complete list of all medications currently in patient possession (all prescribing physicians if present)

- OTC medications, diet, strength, frequency and form
- Inhaled medications, inhalers, nasal sprays
- Parenteral medications, dosage, form and frequency of use
- Topical medications, dose, strength, form and frequency of use
- Reproductive system, history of administration, date and frequency
- Traditional practice items, number and type of prescriptions
- Special products, all brand and generic names used, check for look-alike/sound-alike (LASA) errors
- Allergies, all (including allergic reactions) from, reason for taking, signs or symptoms, date, onset, severity and frequency of use
- Use of alcohol, tobacco, herbal and/or dietary supplements, illicit substances
- Supplemental product labels (e.g., eye, skin, hair, hair removal)
- Medication administration instructions provided, date, frequency of use and reason for initiation
- Medication administration instructions and form, date, frequency and reason for use
- All drug orders, history of use

Review of Proposed HCV Treatment Regimen

- HCV genotype
- HCV viral load
- HCV treatment experience
 - Prior treatment(s)
 - Prior treatment outcome(s)
- National hepatitis C Program Treatment Guidelines
- BSL guidelines www.bsll.ca
- AASLD/DAA guidelines www.hopguidelines.org
- Summary of Product Characteristics (SPC) via www.teva.ca

Drug-drug interaction review

- Using the reference list supplied on the next slide, check each concomitant medication for the potential to interact with the proposed HCV treatment regimen. OR for the concomitant medication to be affected by the HCV medication.
- Review all medication prescribed on the basis of the patient's level of hepatic impairment. Highlight any medications which may be contraindicated in patients with significant hepatic impairment (i.e. cirrhosis).

Reference list source	Summary of all drug-drug interactions
Drugs.com www.drugs.com Drugs.com provides information on drug-drug interactions, drug-food interactions, drug-disease interactions, and drug-laboratory test interactions.	<ul style="list-style-type: none"> • Must be patient's proposed HCV treatment regimen • Only if the patient's concomitant medication • Only if the medication is known to interact • No interaction identified but drug labels do not state drug-drug interaction because all medications are often listed on complete reference labels
Summary of Product Characteristics (SPC) accessed via www.teva.ca (input patient's genotype or other SPC)	<ul style="list-style-type: none"> • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Alcohol • CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole, etc.) • Macrolide antibiotics (e.g., erythromycin, clarithromycin, etc.) • Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, etc.) • Anticholinergics (e.g., atropine, etc.) • Drugs that increase the risk of QT prolongation • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Digoxin • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.)

Reference list source	Summary of all drug-drug interactions
Drugs.com www.drugs.com Drugs.com provides information on drug-drug interactions, drug-food interactions, drug-disease interactions, and drug-laboratory test interactions.	<ul style="list-style-type: none"> • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Alcohol • CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole, etc.) • Macrolide antibiotics (e.g., erythromycin, clarithromycin, etc.) • Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, etc.) • Anticholinergics (e.g., atropine, etc.) • Drugs that increase the risk of QT prolongation • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Digoxin • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.)

Reference list source	Summary of all drug-drug interactions
Drugs.com www.drugs.com Drugs.com provides information on drug-drug interactions, drug-food interactions, drug-disease interactions, and drug-laboratory test interactions.	<ul style="list-style-type: none"> • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Alcohol • CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole, etc.) • Macrolide antibiotics (e.g., erythromycin, clarithromycin, etc.) • Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, etc.) • Anticholinergics (e.g., atropine, etc.) • Drugs that increase the risk of QT prolongation • Concomitant use of the following drugs is contraindicated or requires caution <ul style="list-style-type: none"> • Digoxin • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.) • Digoxin-like immunoreagents (e.g., digoxin, etc.)

Appendix 20: Complex Intervention Toolkit Evaluation Study: Participation invitation email



Hepatitis C Pre-Treatment Pharmacist Assessment (PTPA) Complex Intervention Toolkit Validation Study

Invitation to participate in a research study

Dear _____,

I am currently undertaking a research project with Trinity College and St. James's Hospital, investigating the clinical and cost impact of pharmaceutical care interventions for patients receiving treatment for Hepatitis C with direct acting anti-virals (DAAs). As part of this research project I am developing a complex intervention toolkit (CIT) which aims to drive optimum, safe and cost-effective treatment of Hepatitis C across all healthcare settings.

The initial phase of toolkit design and development has now been completed. As part of the next phase of tool development, a validation study will be completed. The primary aim of this study is to validate the use of the PTPA complex intervention tool for Hepatitis C patients selected for treatment with DAAs. Secondary objectives of this study include determination of the feasibility, acceptability and ability to implement use of the PTPA CIT in everyday clinical practice.

I am emailing today to invite you to participate in this PTPA CIT validation study. I would greatly appreciate your contribution to this project. Participation in the study will involve review of eight sample Hepatitis C patient cases and associated Hepatitis C treatment prescriptions. Participants will have four weeks to complete this process. Please see attached a summary of the study background to date and the validation study protocol.

If you are interested in participating in this working group please email coghlam@tcd.ie by _____. Also, if are any other pharmacists in your service involved in Hepatitis C patient care whom I have not included in this email please forward this invitation to them. As part of this process I am also gathering feedback (via survey) on healthcare professional's opinions on complex intervention tools. I would really appreciate if you could take 5 minutes to complete this short survey, even if you are unable to participate in the validation study. <https://www.surveymonkey.com/r/FKHICY5>

Many thanks in advance for your help.

Kind Regards,

Miriam

Appendix 21: Complex Intervention Toolkit Evaluation Study: Research Ethics Approval

THIS NOTE/PAPER MUST NOT BE USED FOR
PRESCRIPTIONS OR INVOICING PURPOSES



**THE ADELAIDE & MEATH
HOSPITAL, DUBLIN**
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

Ms. Miriam Coghlan,
Hepatitis C Pharmacist,
St. James's Hospital
James's Street
Dublin 8

30th June 2017

Re: Validation of a Hepatitis C pre-treatment pharmacist assessment complex intervention tool.

REC Reference: 2017-06 Chairman's Action (19)

(Please quote reference on all correspondence)

Dear Ms. Coghlan,

The REC is in receipt of your recent application to SJH/AMNCH Research Ethics Committee in which you queried ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your correspondence and considers this to be an audit review with no ethical issues.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 22: Complex Intervention Toolkit Evaluation Study: Survey design

1. What is your role in the healthcare team?
 - a. Consultant physician
 - b. Registrar
 - c. Senior House Officer (SHO)
 - d. Pharmacist
 - e. Clinical Nurse Specialist (CNS)
 - f. General Practitioner
 - g. Other (please specify)
2. Are you involved in the care of patients being treated for Hepatitis C infection?
 - a. Yes
 - b. No
3. In what healthcare setting do you provide care for patients with Hepatitis C infection?
 - a. Hospital outpatient clinics
 - b. Community pharmacy
 - c. Drug treatment clinics
 - d. General practice
 - e. Prison medical centre
 - f. Not applicable
 - g. Other (please specify)
4. How long have you been involved in caring for patients with Hepatitis C?
5. How best would you describe your role(s) in the provision of care to patients with Hepatitis C infection?
 - a. Assessment of patients for suitability for Hepatitis C treatment
 - b. Selecting appropriate Hepatitis C treatment options
 - c. Identification of any potential drug-drug interaction issues between Hepatitis C treatment and patient co-medications
 - d. Prescribing Hepatitis C treatment
 - e. Patient monitoring during Hepatitis C treatment
 - f. Patient education
 - g. Medication counselling
 - h. Medication supply
 - i. Not applicable
 - j. Other, please specify
6. Rank in terms of importance (1= most important) patient specific factors which must be considered by the healthcare team when choosing the optimum HCV treatment regimen for a patient.
 - a. Interpretation of liver disease staging at baseline
 - b. Knowledge of patient concomitant medications and the risk of potentially clinically significant drug-drug interactions.
 - c. Patient renal function
 - d. Patient MELD score
 - e. Patients previous treatment experience
 - f. Up to date information from National and international HCV treatment guidelines
 - g. The decision to co-prescribe ribavirin
 - h. Treatment duration
 - i. Patient's ability to comply with the proposed HCV treatment regimen
 - j. Patient's HCV genotype and viral load
 - k. Patient co-morbidities
7. Rank in terms of importance (1= most important) the service provision factors which may impact the success of HCV DAA therapy for an individual patient.

- a. Location of patient assessment for treatment (Hospital outpatient clinic, GP surgery, community pharmacy, addiction services clinic)
 - b. Location of dispensing of HCV medications
 - c. Provision of medication counselling
 - d. Adherence monitoring
 - e. Adverse effect management
 - f. Regular clinician review while receiving HCV treatment
 - g. Regular CNS review while receiving HCV treatment
 - h. Pharmacist review and phased medication dispensing (including directly observed therapy)
 - i. Cost of HCV treatment
8. Can you define the term complex intervention tool?
 9. Do you use complex intervention tools in your current role? (e.g. STOPP/START criteria, Child Pugh Score for cirrhosis staging) Do you perceive that complex intervention tools are beneficial in healthcare settings? Please explain your answer.
 10. Do you think a complex intervention tool to guide optimum HCV DAA prescribing would be beneficial? If so, how?

Appendix 23: Patient medications identified by pharmacist-led medication reconciliation

Concomitant Medication	No of prescriptions
Abacavir	15
Aciclovir Topical 5%	2
Aclidinium Bromide	1
Adefovir	1
Alendronic acid	9
Alfacalcidol	1
Alfuzosin	1
Alprazolam	7
Amiloride	1
Aminophylline	1
Amitriptyline	4
Amlodipine	12
Amorolfine Topical Solution	1
Anidulafungin	1
Arginine	1
Aripiprazole	1
Aspirin	23
Atazanavir/ritonavir	12
Atenolol	1
Atorvastatin	16
Atovaquone	1
Avanafil	1
Aveeno Lotion®	1
Azapentacene sulfonate sodium	1
Azelastine Nasal Spray	2
Azithromycin	1
Baclofen	3
Beclomethasone Inhaled	10
Bendroflumethiazide/Potassium chloride	1
Berocca Boost®	1
Berocca Performance®	1
Betahistine	2
Betamethasone dipropionate & calcipotriol monohydrate	3
Bisoprolol	8
Botox	1
Bromazepam	1
Buccal midazolam	1
Budesonide Inhaled	3
Bumetanide	3
Buprenorphine 6mg & naloxone 1.5mg	1
Buprenorphine patch	1
Calcium supplements	27

Candesartan	2
Cannabis	5
Carbamazapine	2
Carbocisteine	2
Carbomer Eye Gel	1
Carmellose Eye gel	2
Carsil (Herbal supplement)	1
Cefazolin	1
Ceftriaxone	1
Cetirizine	2
Cholecalciferol	3
Chamomile Tea	3
Chlordiazepoxide	3
Chlorphenamine	3
Chlorthalidone	1
Choline & Inositol	1
Chromium	1
Cider Vinegar	1
Cinchocaine hydrochloride, prednisolone caproate ointment	2
Citalopram	11
Clindamycin/Benzoyl Topical Solution	1
Clobazam	1
Clonidine	1
Clopidogrel	2
Clozapine	1
Cocaine	1
Cod Liver Oil	2
Codeine	3
Co-enzyme Q10	1
Colchicine	1
Complete EFA Nature Aid®	1
Conjugated oestrogens HRT	1
Creon® (Pancreatic Enzymes)	5
Cyclizine	3
Dapagliflozin	1
Dapsone	4
Daptomycin	1
Daraunvir/Ritonavir	25
Denosumab s/c injection	2
Dermol 500 cream®	1
Desloratadine	4
Desogestrel	1
Dexketoprofen	1
Dextromethorphan Cough Syrup	1
Diazepam	51

Diclofenac 1% Topical	6
Diclofenac sodium	5
Digoxin	1
Diltiazem XL	1
Disulfuram	1
Dolutegravir	11
Domperidone	3
Dosulepin	2
Doxazosin	4
Doxycycline	2
Duloxetine	3
Dutasteride	2
Efavirenz	10
Eltrombopag	1
Emtricitabine	53
Enoxaparin	1
Epaderm® ointment	1
Escitalopram	4
Esomeprazole	23
Estradiol Hemihydrate HRT	3
Etanercept	1
Ethinylestradiol, Levonorgestrel (Combined oral contraceptive)	1
Etofenamate Gel	1
Etoricoxib	7
Etravirine	5
Eucerin® Cream	1
Evening Primrose Oil Capsules	3
Facial chemical peel	1
Factor VIII concentrate	4
Felodipine	1
Fentanyl patch	1
Ferrous fumarate	9
Fesoterodine	1
Fexofenadine	4
Finasteride	1
Fish Oils	6
Flurazepam	14
Fluticasone Inhaled	24
Fluticasone Nasal Spray	
Folic acid	6
Formoterol	9
Furosemide	7
Gabapentin	4
Gliclazide MR	8
Glucosamine	3

Green Tea	3
Haloperidol	2
Herbal tea	1
Herbalife Multivitamin®	1
Herbalife Protein Drink®	1
Hydrochlorothiazide	2
Hydrocortisone 1% Topical Cream	1
Hydrocortisone 17-Butyrate Cream	1
Hydromellose Eye Drops	1
Hydroxychloroquine	1
Hydroxycobalamin Injection	2
Hyoscine butylbromide	1
Hypromellose Eye drops	1
Ibandronic acid	1
Ibuprofen	8
Indapamide	3
Insulins	16
Ipratropium inhaled	3
Ispaghula Husk	1
Ivabradine	1
Ketoconazole Shampoo	1
Ketoprofen gel	2
Lacosamide	1
Lacrilube® Eye ointment	2
Lactulose	28
Lamivudine	15
Lamotrigine	2
Lansoprazole	12
Lanthanum Carbonate Hydrate	1
Lercainidipine	6
Levetiracetam	4
Levothyroxine	18
Lidocaine 5% Patch	4
Linseed	1
Liraglutide	1
Lisinopril	1
Lithium	3
Liver Tea	1
Lofepamine	1
Loperamide	3
Lopinavir/ritonavir	1
Lorazepam	2
L-ornithine-L-aspartate sachet	1
Losartan	1
Lymecycline	1

Macrogol laxative	13
Macushield®	1
Magnesium Supplement	2
Manuka Honey	2
Mebeverine	1
Medroxyprogesterone	3
Meloxicam	1
Menopace®	1
Mesalazine	1
Metformin	14
Methadone	85
Methotrexate	1
Methylprednisolone	1
Metronidazole	1
Miconazole/Hydrocortisone Topical Cream	1
Midazolam Buccal	1
Milk Thistle	4
Mirabegron	2
Mirtazepine	23
Mometasone ointment	5
Montelukast	1
MOR EPA® fish oil supplement	2
Multivitamin combinations	13
Naproxen	1
Nebivolol	1
Nicotine replacement therapy- Gum	2
Nicotine replacement therapy-Patch	3
Nicotine replacement therapy-Spray	1
Nitrofurantoin	1
Norethisterone	2
Nutrition 1: Organic power greens®	1
Olanzapine	11
Olmesartan	3
Omeprazole	33
Ondansetron	1
Orlistat	1
Osteophos® Sachet	2
Osteosupport® Supplement	1
Oxcarbazepine	2
Oxybutynin	3
Oxycodone	4
Pantoprazole	9
Paracetamol	15
Paracetamol/Codeine	7
Paracetamol/Tramadol	3

Paroxetine	1
Pentamidine inhaled	1
Peppermint Tea	1
Perampanel	1
Perindopril	7
Pharmaton®	6
Phenobarbital	3
Phenoxyethylpenicillin	1
Phenytoin	2
Phytomenadione	1
Phytosoy® (Soy isoflavonoids)	1
Pioglitazone	1
Piperacillin/Tazobactam	1
Polyvinyl Alcohol Eye Drops	1
Potassium citrate sachets	1
Pramipexole	1
Pravastatin	2
Prednisolone	1
Pregabalin	12
Prochlorperazine	2
Procyclidine	1
Promethazine	1
Propranolol	33
Propylene Glycol Eye Drops	1
Protein supplements	3
Quetiapine	3
Quinine Sulphate	4
Raltegravir	35
Ramipril	13
Ranitidine	6
Rasagiline	2
Revive Active Sachets®	1
Rifaximin	10
Rilpivirine	4
Risedronate	1
Risperidone	2
Rituximab	1
Ropinirole	3
Rosehips	2
Rosuvastatin	1
Rotigotine	1
Salbutamol Inhaled	21
Salicylic Acid, Coconut Oil, Distilled Coal Tar (Shampoo)	1
Salmerterol Inhaled	13
Senna	6

Sertraline	6
Sevelamer hydrochloride	1
Sildenafil	8
Simvastatin	2
Sinemet	2
Sitagliptin	2
Sodium valproate	3
Solifenacin	1
Sotalol	1
Spirolactone	25
Stem cell facial treatment	1
Strontium ranelate	1
Sulfamethoxazole and trimethoprim	6
Sulpiride	1
Sumatriptan	2
Sylminium (Herbal product)	1
Tacrolimus	1
Tadalafil	4
Tamsulosin	3
Taurine eye drops	1
Temazepam	2
Tenofovir	59
Teriparatide S/C	1
Thiamine	12
Tinzaparin	3
Tiotropium Inhaled	8
Tramadol	8
Tranexamic acid	1
Triazolam	1
Trimipramine	1
Udo's Choice Super 8 Probiotic®	1
Umeclidinium inhaled	1
Ursodeoxycholic acid	1
UV Light therapy	1
Valaciclovir	4
Valerian Tea	1
Valsartan	8
Venlafaxine	6
Vilanterol	2
Vitamin B Complex	3
Vitamin C	10
Vitamin D	4
Warfarin	4
Well Women® Vitamin	1
Wheatgrass	2

Zinc	3
Zoledronic acid IV	4
Zolpidem	13
Zopiclone	35

Appendix 24: Epilepsy Patient Cases

Patient	DAA Regimen	AED Regimen	DDI Potential	DDI Management Plan	Patient outcome
1	PrOD/RBV	Sodium valproate	Valproate is metabolised by multiple UGTs with minor involvement of CYP enzymes. Induction of glucuronidation by ritonavir may result in a decrease in valproate concentrations.	Therapeutic drug monitoring (TDM) for sodium valproate at baseline of treatment, 7 days thereafter and monthly through treatment.	The dose of sodium valproate was increased two weeks into treatment based on a low TDM result. SVR 12 achieved
2	SOF/LDV/RBV	Carbamazepine	Induction of P-gp by carbamazepine may significantly decrease plasma concentrations of ledipasvir and sofosbuvir resulting in loss of efficacy and potential virological failure.	Carbamazepine discontinued under monitoring from the patient medical team.	No seizure activity during HCV treatment. SVR 12 achieved
3	SOF/LDV	Levetiracetam	Nil DDI potential	N/A	SVR 12 achieved
4	SOF/DCV/RBV	Sodium Valproate	Nil DDI potential	N/A	SVR 12 achieved
5	SOF/LDV/RBV	Sodium Valproate	Nil DDI potential	N/A	SVR 12 achieved
6	SOF/VEL	Lamotrigine	Nil DDI potential	N/A	SVR 12 achieved
7	PrOD/RBV	Lamotrigine	Lamotrigine is a substrate of UGT1A4. A reduction in lamotrigine exposure is possible with PrOD.	Patient DAA regimen changed to SOF/LDV to avoid any DDI with AED therapy.	SVR 12 achieved
8	SOF/DCV	Sodium valproate	Nil DDI potential	N/A	SVR 12 achieved
9	PrOD/RBV	Levetiracetam Topiramate	Nil DDI potential	N/A	SVR 12 achieved
10	SOF/DCV	Eslicarbazepine Perampanel Sodium valproate Lacosamide Clobazam	Co-administration is contraindicated. Eslicarbazepine is expected to decrease daclatasvir concentrations and may lead to the loss of efficacy of daclatasvir.	Neurology services currently cannot remove eslicarbazepine from the AED regimen due to ongoing seizure activity.	Patient currently untreated for HCV. Regular review with neurology and hepatology to consider options for treatment and potential for AED switch.

11	SOF/LDV	Phenytoin	Co-administration is not recommended. Induction of P-gp by phenytoin may significantly decrease plasma concentrations of ledipasvir and sofosbuvir resulting in loss of efficacy and potential virological failure.	Patient switched to levetiracetam through titrated dosing regimen.	SVR 12 achieved
12	SOF/LDV	Carbamazepine	Induction of P-gp by carbamazepine may significantly decrease plasma concentrations of ledipasvir and sofosbuvir resulting in loss of efficacy and potential virological failure.	Patient switched to levetiracetam through titrated dosing regimen.	SVR 12 achieved
13	SOF/LDV/RBV	Sodium valproate Levetiracetam	Nil DDI potential	N/A	SVR 12 achieved
14	SOF/DCV/RBV	Levetiracetam Oxcarbazepine	Co-administration is contraindicated. Oxcarbazepine is expected to decrease daclatasvir concentrations due to induction of CYP3A4 by oxcarbazepine and may lead to the loss of efficacy of daclatasvir. Sofosbuvir should not be used with oxcarbazepine, a potent intestinal P-gp inducer, as it is likely to reduce sofosbuvir concentrations resulting in potential sub therapeutic effect.	Treatment with oxcarbazepine tapered and discontinued. Patient continued on levetiracetam during DAA therapy.	SVR 12 achieved. No seizure activity reported during HCV treatment.
15	SOF/LDV/RBV	Levetiracetam	Nil DDI potential	N/A	SVR 12 achieved
16	PrOD	Phenytoin Phenobarbital	Co-administration is contraindicated. PrOD exposure may decrease due to induction of CYP3A4 by phenobarbital. In addition, a clinically significant decrease in phenobarbital and phenytoin plasma exposure may occur.	Dose tapering regimen ongoing.	Hepatitis C treatment not yet initiated.
17	SOF/LDV/RBV	Levetiracetam	Nil DDI potential	N/A	SVR 12 achieved

18	SOF/LDV/RBV	Sodium valproate	Nil DDI potential	N/A	SVR 12 achieved
19	SOF/LDV/RBV	Levetiracetam	Nil DDI potential	N/A	SVR 12 achieved
20	SOF/LDV/RBV	Lamotrigine Phenobarbital	Co-administration is not recommended. Induction of P-gp by phenobarbital may significantly decrease plasma concentrations of ledipasvir and sofosbuvir resulting in loss of efficacy and potential virological failure.	Treatment with phenobarbital tapered and discontinued. Patient continued on levetiracetam during DAA therapy.	SVR 12 achieved
21	SOF/DCV/RBV	Levetiracetam Lamotrigine	Nil DDI potential	N/A	SVR 12 achieved
22	SOF/DCV	Carbamazepine	Co-administration is contraindicated. Carbamazepine is expected to decrease daclatasvir concentrations due to induction of CYP3A4 and may lead to the loss of efficacy of daclatasvir. Co-administration with sofosbuvir is also not recommended. Carbamazepine is a potent inducer of P-gp and may significantly decrease sofosbuvir concentrations. This may result in loss of efficacy and potential virological failure.	Patient switched to levetiracetam through titrated dosing regimen.	SVR 12 achieved

Appendix 25: Complex intervention toolkit: Design and Development: Initial toolkit draft format

Version 1.0:

Review of patient clinical parameters and co-morbidities:

- Age
- Weight
- Sex
- Laboratory markers
- List of co-morbidities

Medication reconciliation (including allergy status)

Information sources used:

- Patient interview
- Patient list
- Patient's own medications
- General practitioner
- Community pharmacy
- Drug treatment centre
- Patient relative or carer
- Patient medical notes
- Electronic patient records
- Medical notes from other healthcare providers that a patient may attend

*It is important to remember that patients may be obtaining medications from multiple sources including:

- Medication prescribed by a general practitioner/specialist/dentist.
- Over the counter in a community pharmacy.
- Online
- Herbal shops
- Sports shops
- Supermarkets
- Relatives or friends
- Illicit drugs
- Homeopathic
- Foods: Grapefruit and herbal teas including green tea.
- Allergy status

When obtaining information relating to medication taken by a patient please ensure all of the following information is checked:

1. Oral medications: Dose, strength, frequency and form
2. Inhaled medications: Inhalers, nasal sprays
3. Eye preparations: Dose, strength, form and frequency of use.
4. Topical products: Dose, strength, form and frequency of use.
5. Injections/infusions: Route of administration, dose and frequency
6. Transdermal patches: Dose, number applied and frequency of use.
7. Herbal products: Full brand name, store where purchased, reason for taking, dose, form and frequency of use.
8. Online: Full product name, website purchased from, reason for taking, reason for buying online, form, dose, strength and frequency of use.
9. Over the counter medicines: Product name, reason for use, dose, form and frequency.
10. Supermarkets: Product name, reason for use, dose, form and frequency.
11. Sports shops: Full product name of supplements purchased, dose, frequency of use and

reason for purchase.

12. Homeopathic medicines: Names of products used, form, dose, frequency and reason for use.
13. Illicit: Drug name, frequency of use.

A complete list of all information collected as part of the medication reconciliation should be documented in the patient medical notes either paper or electronic.

Use the information obtained as part of the medication history to calculate the medication regimen complexity index (MRCI) for each patient. Patient's identified as having high MRCI scores may require additional medication education sessions or increased medication adherence aid use.

Drug-drug interaction review

- Hepatitis C genotype:
- Proposed HCV treatment regimen:
- Proposed treatment duration:
- Factors to consider with DDIs: severity, manageability, risk/benefit assessment and patient related risk factors.
- Using the reference list check each concomitant medication for the potential to interact with the proposed HCV regimen.
- For all interactions checks where the potential for an interaction to occur was identified or was unknown, document the action taken and any monitoring plan which is to be put in place.
- Review all medication prescribed based on the patient's level of hepatic impairment. Document if any medication prescribed for this patient is cautioned or contra-indicated in hepatic impairment.
- DDI report & summary: Provide a summary of all relevant DDIs to the HCV therapy prescriber along with suggested management plans for these interactions. Also highlight any concomitant medications which may be cautioned in patients with hepatic impairment.
- How you interpret DDI data and its clinical relevance in any patient case depends on your skill base and experience.

MRCI

Use the information obtained as part of the medication history to calculate the medication regimen complexity index (MRCI) for each patient. Patient's identified as having high MRCI scores may require additional medication education sessions or increased medication adherence aid use.

Version 1.1: Hepatitis C Pharmaceutical Care Process Complex Intervention Toolkit

Step 1: Patient baseline characteristics

Patient Age	_____ yrs	Gender	Male/Female
Patient Weight	_____ kg		
Hepatitis C Genotype		HCV Viral Load	
Liver Disease Staging	Fibroscan: _____ kPa	Biopsy: _____	Ultrasound/CT: _____
Co-morbidities (ICD-10 Classification)	Gastro-intestinal	Endocrine	Malignancy/Immunosuppression
	Cardiovascular	Obs, Gyn Urinary	Musculoskeletal/Joint Diseases
	Respiratory	Haematology	Ophthalmology
	Infection	Skin	ENT
	CNS	Psychiatry	
Allergy Status			
Baseline Laboratory Markers	AST	ALT	Bilirubin
	Albumin	Gamma GT	Alpha-feto protein
	INR	Platelets	Haemoglobin
Renal Function	Cockcroft & Gault		
Hepatic Function Measurement in patients with liver cirrhosis	Child Pugh Score	MELD Score	APRI Score

Step 2: Medication Reconciliation

Information sources used: Please tick

Patient interview	Community Pharmacy	Electronic patient records
Patient medication list	Drug Treatment Centre	Other healthcare providers
Patient's own medications	Patient carer/relative	
GP	Patient medical notes	

Confirm with the patient if they obtain medication from any of the [sources listed here](#).

When obtaining information relating to medication taken by a patient please ensure [information on all potential medication forms](#) is obtained.

Completed list of patient concomitant medications:

Drug Name	Form	Route	Dose	Frequency

Calculate the patient's [medication regimen complexity index \(MRCI\)](#) score to identify need for additional medication counselling and treatment adherence supports.

Step 3: Review of the proposed HCV treatment regimen

HCV Genotype			HCV VL	
HCV Treatment History		Treatment naïve	Treatment experienced	
Previous treatment regimens				
Previous Treatment response		Relapse	Partial response	Null responder
Proposed HCV Regimen	Sofosbuvir/ledipasvir		PROD (3D)	Sofosbuvir/Simeprevir
	Sofosbuvir/daclatasvir		PRO (2D)	Grazoprevir/Elbasvir
	IFN/RBV/Sofosbuvir		IFN/RBV/Simeprevir	Sofosbuvir/Velpatasvir
	Other: _____			
Is ribavirin co-prescribed?		Yes		No
Proposed treatment duration	8 weeks		12 weeks	
	24 weeks		Other: _____	
Is the proposed treatment regimen licensed?		Yes		No
Is the proposed treatment duration licensed?		Yes		No
Does the proposed treatment regimen meet National/EU treatment guidelines?		Yes		No

Step 4: Drug-drug interaction review

See [reference resource list](#).

Results of drug-drug interaction review:

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan	Use in hepatic impairment

Recommendations/Suggestions/Feedback from stakeholder research group

28/2/2106 – 4/3/2017: Tabular format of the toolkit was developed and circulated for review to the group by the lead researcher. Factors suggested for consideration to be included by the group were:

- Addition of APRI score
- Na+ result inclusion
- ICD 10 classification of co-morbidities to be considered for inclusion
- Add in a date box beside the liver disease staging section
- Add in a date box beside the patient weight recorded
- Add in a date box beside the blood results recorded
- Links to additional resources if needed to be added as hyperlinks
- Does the proposed regimen meet national guidelines? Add in tick box for this.
- Addition of space to document previous HCV treatment regimens and associated outcomes.
- Relative and friend's category removed from medication source list.
- Removal of sections from the toolkit relating to pharmacist-led interventions that occur at the beginning of and during Hepatitis C treatment. These interventions will be assessed via a separate research project. The focus of this research project is pharmacist-led pre-treatment interventions.

16/6/2016:

- Date box added beside HCV viral load result.
- Proposed HCV treatment options section to be designed as a tick box.
- Changed the co-morbidity section from a tick box to a blank section for users to write in co-morbidities as the potential list is endless. Idea of ICD-10 discarded by the group.
- Incorporate regimen treatment guidelines into the toolkit rather than having a link to the full guidelines document. Decided against this as the guidelines were undergoing continuous change in 2016/2017 as the toolkit was being developed.
- Add tick box beside information sources used to complete medication reconciliation
- Change in layout of medication list collected during medication reconciliation. Separate columns for form, route, dose and frequency removed. Replaced by free text box. Separate sections to denote medication dispensed or received from different sources retained.
- Box to document stage of cirrhosis added.
- Removal of the medication regimen complexity index (MRCI) tool from the toolkit.

22/6/2016:

- Change of layout in section 1 proposed: Patient baseline characteristics: Put in a stop rule in the tool for patients with MELD >18 or CTP B/C. Decision made not to add this stopping rule by the stakeholder research group.
- Decision not to add treatment guidelines to the toolkit is affirmed by the group.
- Box to document stage of cirrhosis removed.
- Decision question added in at the bottom of patient characteristics section. “Based on the above information does this patient have cirrhosis?”. Yes/No
- Decision question added in at the bottom of patient characteristics section. “Has this patient had an episode(s) of hepatic decompensation? Yes/No

25/7/2016:

- Addition of dialysis, yes/no box.
- Date box to be added beside creatinine clearance.
- Decision question at the bottom of patient characteristics section. “Based on the above information does this patient have cirrhosis?”. Answer choice amended to include another potential answer, “Not determined”.
- Decision question at the bottom of patient characteristics section. “Has this patient had an episode(s) of hepatic decompensation?” Answer choice amended to include another potential answer, “Not determined”.
- Question added to the review of the proposed HCV treatment regimen. “If treatment experienced with DAAs please documented resistance profile results.”

28/7/2016:

- Consider interchanging APRI with FIB-4 score.
- Addition of Hepatitis B markers to the patient characteristics section with date of results
 - Hepatitis B core antibody, surface antigen, surface antibody result.
 - e antigen positive and e antigen negative tick boxes to be completed if appropriate.
 - HBV viral load column added to be completed if appropriate.
- HIV screening result and date added to the patient characteristics section.
- Column added to the table for the completed list of patient pre-treatment medications and supplements, to identify “potential for interaction with DAAs”. Yes/No/Unknown.
- Separate section to document outcomes of MDT report discussion and plan added.
- Patient assessment completed by signature and date section added to the end of the toolkit proforma.
- Toolkit abbreviation list and reference source list compiled and added to the toolkit.

11/01/2017- 18/01/2017

- Addition to completed to record route of acquisition and year of HCV acquisition added to the patient characteristics section.
- Addition of column to document current alcohol intake.
- Addition of column to the completed list of patient pre-treatment medications and supplements, to document contraception planning for both patient and partner(s).
- Addition of four questions to the patient baseline characteristics section.
 - Presence or history of ascites: Yes/No
 - Presence or history of encephalopathy: Yes/No
 - Presence or history of portal hypertension: Yes/No
 - Presence or history of varices: Yes/No
- Change of use of APRI score to FIB-4 score

Final version of PTPA complex intervention toolkit

Step 1: Patient baseline characteristics

Patient Age	yrs		Gender			
Patient Weight	kg		Date of weight			
Hepatitis C Genotype			HCV Viral Load		Date:	
First Diagnosed			Route of acquisition			
Liver Disease Staging	Fibroscan: _____kPa Date:		Biopsy: _____ Date:		Ultrasound/CT: _____ Date:	
Co-morbidities						
Alcohol Intake						
Allergy Status						
Baseline Laboratory Markers	AST		ALT		Bilirubin	
	Na ⁺		Platelets		Creatinine	
Date of Labs:	Albumin		Gamma GT		Alpha-feto protein	
	INR		Dialysis	Y/N	Haemoglobin	
Renal Function	Cockcroft & Gault				Date	
Hepatitis B Markers	Core Antibody				Surface Antibody	miU/ml
	Surface Antigen				HBV viral load	
	Hepatitis B e Antigen (If HBV infection confirmed)				e Antigen positive	e Antigen negative
HIV Ag/Ab Combo						
Based on the available information does this patient have cirrhosis? If yes, please complete below questions			Yes	No	Not determined	
If cirrhotic, has this patient had an episode(s) of hepatic decompensation?			Yes	No	Not determined	
Ascites	Yes / No		Encephalopathy		Yes / No	
Varices	Yes / No		Portal HTN		Yes / No	

Hepatic Function Measurement in patients <u>with liver cirrhosis</u>	Child Pugh Score	MELD Score	FIB-4 Score
Date:			

Step 2: Medication Reconciliation

When obtaining information relating to medication taken by a patient please ensure information on all potential medication forms is obtained. (Oral medications, topical agents, transdermal patches, inhalers, eye drops, herbal teas etc.)

Information sources used to determine the patient's current medications:

Patient interview		Contact with Community Pharmacy		Patient hospital medical notes	
Patient's own medication list		Contact with Drug Treatment Centre		Electronic patient records	
Patient's own medications		Contact with GP		Other healthcare providers	
Contact with a patient carer/relative					

Source	Medication List	Potential for DDI
Community pharmacy		
Drug treatment clinic		
Hospital Outpatient Clinic		
Healthfood Shop /Supermarket/Gym supplements		
Online		
Illicit		
Other		
Contraception planning for both patient and partner(s) while on Hepatitis C treatment.		

Step 3: Review of the proposed HCV treatment regimen

HCV Genotype		HCV VL		Date	
HCV Treatment History	Treatment naïve			Treatment experienced	
Previous treatment regimens					
Previous Treatment response	Relapse	Partial response to IFN/RBV	Null responder	Viral breakthrough on treatment	
If treatment experienced with DAAs please document resistance profile					
Proposed treatment regimen					
Is ribavirin co-prescribed?	Yes			No	
Proposed treatment duration	8 weeks			12 weeks	
	24 weeks			Other:	
Does the proposed treatment regimen meet National treatment guidelines?	Yes			No	

Step 4: Drug-drug interaction review (See reference resource list)

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan

Outcomes of MDT report discussion and plan:

CIT completed by: _____ **Date:** _____

Appendix 26: Worked example of PTPA toolkit in use

Hepatitis C Pharmaceutical Care Process Complex Intervention Toolkit

Step 1: Patient baseline characteristics

Patient Age	45 yrs		Gender		Male	
Patient Weight	66 kg		Date of weight		15/05/2019	
Hepatitis C Genotype	3		HCV Viral Load		1.1 million	Date: 04/2019
First Diagnosed	2007		Route of acquisition		PWID	
Liver Disease Staging	Fibroscan: 9.5kPa Date: 16/04/2019		Biopsy: Nil Date: n/a		Ultrasound/CT: Fatty infiltration Date: 01/2019	
Co-morbidities	Asthma (Note patient is a current smoker, 20/day x >25 years) Depression History of seizures secondary to benzodiazepine withdrawal Deep vein thrombosis (2012) secondary to injecting drug use: Treated with tinzaparin x 6 months					
Alcohol Intake	Now abstinent but with a history of previous excess					
Allergy Status	No known drug allergies					
Baseline Laboratory Markers	AST	45	ALT	37	Bilirubin	10
	Na ⁺	141	Platelets	190	Creatinine	78
Date of Labs: 04/2019	Albumin	43	Gamma GT	55	Alpha-feto protein	1.9
	INR	1.0	Dialysis	No	Haemoglobin	15.2
Renal Function	Cockcroft & Gault		99ml/min		Date	15/05/2019
Hepatitis B Markers (04/2019)	Core Antibody		Negative		Surface Antibody	125mIU/ml
	Surface Antigen		Negative		HBV viral load	n/a
	Hepatitis B e Antigen (If HBV infection confirmed)				e Antigen positive: n/a	e Antigen negative: n/a
HIV Ag/Ab Combo			Negative (04/2019)			
Based on the available information does this patient have cirrhosis? If yes, please complete below questions			No			
If cirrhotic, has this patient had an episode(s) of hepatic decompensation?			N/A			
Ascites	N/A		Encephalopathy		N/A	
Varices	N/A		Portal HTN		N/A	

Hepatic Function Measurement in patients with liver cirrhosis	Child Pugh Score	MELD Score	FIB-4 Score
Date: 15/05/2019	N/A	N/A	1.75

Step 2: Medication Reconciliation

When obtaining information relating to medication taken by a patient please ensure information on all potential medication forms is obtained. (Oral medications, topical agents, transdermal patches, inhalers, eye drops, herbal teas etc.)

Information sources used to determine the patient's current medications:

Patient interview	Yes	Contact with Community Pharmacy	Yes	Patient hospital medical notes	Yes
Patient's own medication list		Contact with Drug Treatment Centre	Yes	Electronic patient records	Yes
Patient's own medications		Contact with GP		Other healthcare providers	
Contact with a patient carer/relative					

Source	Medication List	Potential for DDI
Community pharmacy	Salbutamol inhaler 100mcg i-ii puffs QDS/PRN Seretide Diskus i puff BD Sertraline 100mg mane Levetiracetam 500mg BD	Nil DDI with SOF/VEL or G/P
Drug treatment clinic	Methadone 40mg once daily. Collects supply from clinic twice weekly. Flurazepam 30mg nocte Diazepam 5mg twice daily	Nil DDI with SOF/VEL or G/P
Hospital Outpatient Clinic	N/A	N/A
Health food Shop /Supermarket/Gym supplements	Vitamin C Multivitamin: Centrum Antacids	Potential for DDI with SOF/VEL
Online	Nil	N/A
Illicit	Cannabis once/twice per week	Nil DDI with SOF/VEL or G/P
Other	Nil	N/A
Contraception planning for both patient and partner(s) while on Hepatitis C treatment.	Not in a relationship	N/A

Step 3: Review of the proposed HCV treatment regimen

HCV Genotype	3	HCV VL	1.1 million	Date	04/2019
HCV Treatment History	Treatment naïve: Yes		Treatment experienced: No		
Previous treatment regimens	N/A				
Previous Treatment response	Relapse	Partial response to IFN/RBV	Null responder	Viral breakthrough on treatment	
If treatment experienced with DAAs please document resistance profile	N/A				
Proposed treatment regimen	SOF/VEL				
Is ribavirin co-prescribed?	Yes		No		
Proposed treatment duration	8 weeks		12 weeks		
	24 weeks		Other:		
Does the proposed treatment regimen meet National treatment guidelines?	Yes		No		

Step 4: Drug-drug interaction review (See reference resource list)

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan
Antacids	May alter gastric pH which may impact velpatasvir absorption.	Patient advised to separate antacid use (Gaviscon) from SOF/VEL by 4 hours. Confirm with patient that they are not using any other medications for the stomach or for indigestion. (e.g. PPI)	Counsel patient on these two interaction issues prior to treatment start and at each visit to clinic to collect medications. Provide written information to re-enforce time gap.
Multivitamin: Confirmed as Centrum®	Some constituents within the multivitamin may alter gastric pH which may impact velpatasvir absorption.	Patient advised to separate multivitamin use from SOF/VEL by 4 hours.	

Outcomes of MDT report discussion and plan:

All DDIs identified, with plans in place. Re-enforce dose time separation at each visit to clinic.

PTPA toolkit completed by: MC

Date: 15/05/2019

Appendix 27 PhD Viva Presentation



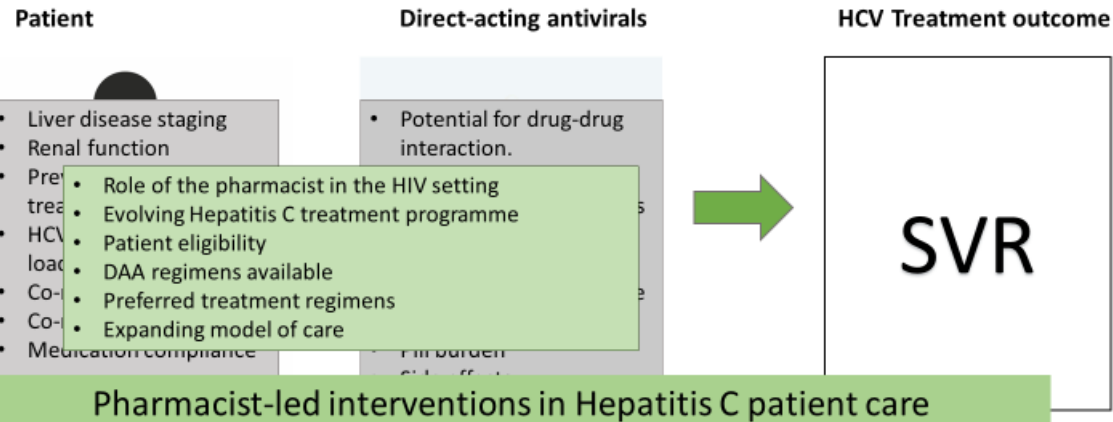
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The clinical impact and outcomes of pharmacist-led interventions in the outpatient model of care for Hepatitis C patients and their development into a novel complex intervention toolkit.

Miriam Coghlan BSc (Pharm), MSc.
21st January 2020

Hepatitis C Treatment



Research Questions

- What role does the pharmacist play in optimising Hepatitis C treatment outcomes?
- Can a novel complex intervention toolkit, incorporating pharmacist-led interventions facilitate healthcare professionals in selecting the optimum HCV treatment regimen when assessing patients for HCV treatment?



Research Outline

Part 1

Study 1 - Medication reconciliation

Study 1a - Clinical significance of medication reconciliation variances

Study 2 - Complementary and alternative medicines (CAM) among HCV seropositive patients

Study 3 - DDIs between patient co-medications and DAAs

Study 4 - Patients with chronic HCV infection and co-morbid epilepsy treated with DAAs

Part 2

Study 1 - Design, development and optimisation of the Hepatitis C pre-treatment pharmacist assessment (PTPA) toolkit

Study 2 - Feasibility and acceptability of the PTPA complex intervention toolkit

Study 3 - PTPA Pilot Study

Study 4 – PTPA Evaluation Study



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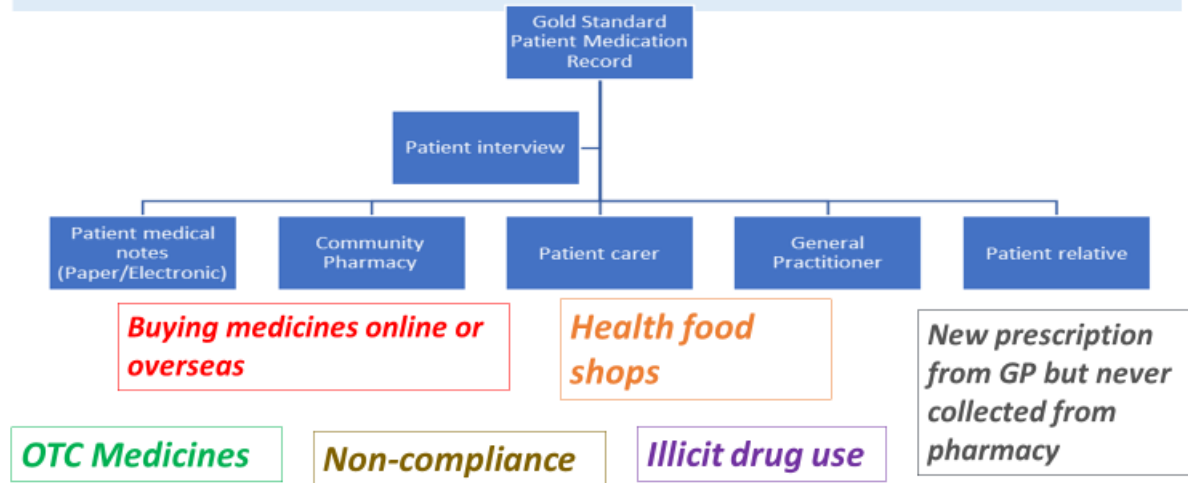
Part 1

Descriptive studies



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Method – Medication reconciliation process



Study 1 - Results

- Medication variances identified in 74% of patients of the study cohort
- Medication omission (87%) the most frequent type of medication variance identified
- Patient factors found to be associated with variance occurrence included co-morbid liver cirrhosis, HIV co-infection and greater than three co-medications ($p < 0.05$)
- Average time to complete medication reconciliation: 19 minutes



Study 1a - Assessment of the clinical significance of medication reconciliation variances

- **Study Background:** Nested study to assess clinical significance of medicines reconciliation variances
- **Method**
 - Cross-sectional observational study
 - Three pharmacists recruited to complete the process of reviewing & grading the potential severity of medication variances identified in all 50 study cases
 - A Visual Analogue Scale (0-10) was used to grade the variances
- **Study population:** 50 patients selected from medication reconciliation study cohort using a random sampling method
- **Results**
 - A total of 98 medication variances were assessed for potential severity
 - VAS scores of >7 were assigned to 16 medication variance episodes
 - Medications used in the treatment of epilepsy accounted for four high risk variance episodes



Conclusions & Implications for Studies 1&1a

- **What was known prior to this study?**
 - Studies to date have advocated the beneficial effects of medication reconciliation at the point of hospital admission
 - No published research which has examined the HCV outpatient medication reconciliation process, types of variance identified and their associated significance
- **What is the added value of this study?**
 - This research provides valuable information on the process of medication reconciliation in an outpatient setting
 - It highlights that the rate of medication variances in the outpatient setting is similar or higher to that reported in the inpatient medication process
- **Implications of the new findings?**
 - It is through the process of pharmacist-led medication reconciliation that an accurate patient medication list can be obtained to ensure the most appropriate HCV DAA treatment is selected and all potential DDIs are effectively managed



Study 2 - An assessment of patient knowledge and attitudes towards complementary and alternative medicines (CAM) among HCV seropositive patients

- **Study Background**

- High rate of use of multivitamins, mineral supplements and other complementary and alternative medicines (CAM) was identified during the medication reconciliation study
- Growing risk of DDIs between CAM products and HCV DAAs highlighted in published research
- No published research on CAM use among HCV patients in the DAA era

- **Study method**

- Quantitative survey design to identify, quantify, describe and categorise use of CAM
- Measurement of patient perceptions about CAM use
- One-to-one semi-structured interviews, incorporating a 30 item survey and a self-reported quality of life rating (0-10)

- **Study population:** Convenience sample of 50 patients

- Ethical approval (St. James's & Tallaght Hospitals REC 2017- 05, REC 2019-04)



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Study 2 - Results

- 44% reported use of CAM (N = 22)
- Most commonly reported CAM products were gym supplements (36.4%), herbal teas (36.4%), milk thistle (13.6%) and multivitamins (13.6%)
- Rationale for use: To improve general health (27.3%) and gym workout results (22.7%)
- Sources of information: Family & friends (68.2%) and on-line (18.2%)
- Purchase points: Health food shops (68.2%), community pharmacies (18%), on-line (13.6%)
- No associations between CAM use and self-reported quality of life scores ($p=0.892$), nor specific co-morbidities were found
- Satisfaction among CAM users (0-10) = 4.7 (Range 1-10)
- Third level education found to be associated with CAM use (Richmond and Ferrucci *et al*)
- DDI risk: St. John's Wort, high dose garlic supplements, spirulina and weight loss tea



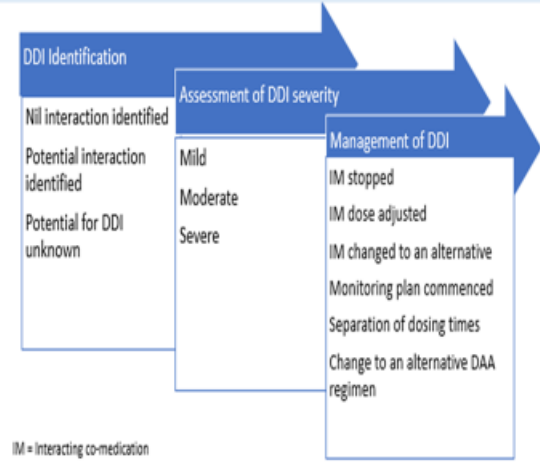
Study 2 - Conclusions & Implications

- **What was known prior to this study?**
 - Use of CAM was recognised in the interferon era
 - No published research on CAM use among HCV patients in the DAA era
- **What is the added value of this study?**
 - First research identifying the rate of CAM use among HCV patients in the DAA era
 - A high proportion of patients reported CAM product use
 - The majority of patients using CAM products do so in conjunction with conventional medicine
 - Patients do not always disclose use of CAM to HCPs
 - There is the potential for DDI between CAM products and HCV DAA therapy
- **Implications of the new findings?**
 - Healthcare professionals caring for people with HCV infection should specifically ask patients about their use of these products during consultations
 - It is important that the potential for DDI between CAM products is assessed with patient co-medications including when DAA therapy is being prescribed



Study 3 - Assessment of the potential DDIs between patient co-medications and DAAs

- **Study Background**
 - Research assessing risk of DDI with DAAs largely theoretical rather than real-world studies
 - No published research describing pharmacist-led management strategies for DAA DDIs and patient outcomes
- **Study method**
 - **Observational cohort study**
 - Prevalence, type & severity of DDIs between DAAs and identified patient co-medications
 - Standardised DDI reference list
 - Determine pharmacist-developed DDI management strategies
 - Assess the rate of acceptance, among prescribers, of the pharmacist-developed DDI management strategies
 - Ethical approval: (St. James's & Tallaght Hospitals REC 2016-05)
- **Study population:** N = 300 patients



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Clarithromycin	●	■	●	■	●	■
Ethosuximide	●	■	●	■	●	■
Levodopa/Carbidopa	●	■	●	■	●	■
Clonidine/PTU/ + DDA	●	■	●	■	●	■
Simvastatin	●	■	●	■	●	■
Sildenafil	●	■	●	■	●	■

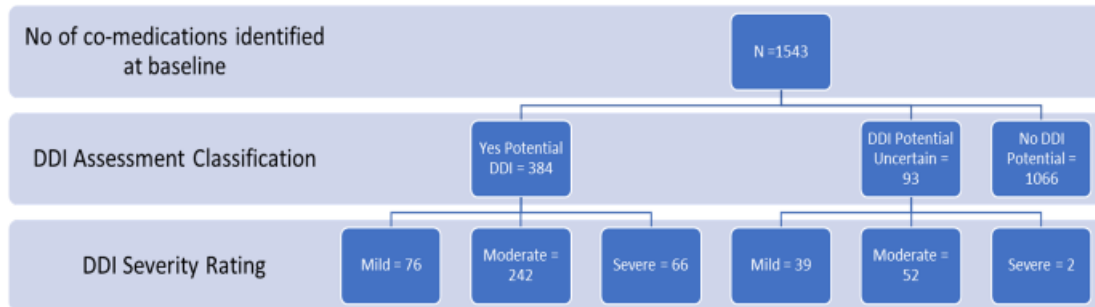
Stockley's Drug Interactions Twelfth edition Edited by Claire L. Preston

HPRA An tÚdarás Rialála Táirgí Sláinte Health Products Regulatory Authority

ABOUT US MEDICINES VETERINARY MEDICAL DEVICES BL

Study 3 - Results

Of 1543 medications assessed for DDI potential, 477 were identified as a potential or unknown DDI risk



Study 3 - Results

Potential DDI Management Strategy	Number of DDI episodes
Discontinuation of an interacting medication during HCV therapy	90 episodes affecting 52 patients
Dose adjustment of an interacting co-medication	60 episodes affecting 52 patients
A change in the interacting medication to an alternative in class or in clinical effect	72 episodes affecting 51 patients
Initiation of a monitoring plan	173 episodes affecting 98 patients
A dose time separation strategy	72 episodes affecting 50 patients
Consideration of an alternative HCV treatment regimen	10 episodes affecting patients

- The rate of acceptance of pharmacist-led DDI management plans was high overall, at 96.9% (N = 462)
- In cases of potentially severe DDI cases 100% of pharmacist-developed management plans were accepted



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Study 3 - Conclusions & Implications

- **What was known prior to this study?**
 - No published research describing pharmacist-led management strategies for DAA DDIs and patient outcomes
- **What is the added value of this study?**
 - Pharmacist-led DDI review identified that a significant proportion of patients were at risk of clinically significant DDIs
 - DDIs, classified as potentially severe, affected 14% of the study population
 - High acceptance rate pharmacist-led DDI management plans (96.9%)
- **Implications of the new findings?**
 - Pharmacist-led medication reconciliation and DDI assessment are key roles in the stewardship of DAAs to ensure optimum patient outcomes and to reduce the risk of drug-related problems



An Analysis of the Medication Reconciliation Process in an Outpatient Clinic Setting
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 Pharmacy Department, St. James's Hospital, School of Medicine, Trinity College Dublin, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin.

Introduction
 Medication reconciliation (MedRec) is the process of identifying and maintaining an accurate and detailed list of all prescribed and nonprescribed medicines a patient is taking. Pharmacist-led interventions in Hepatitis C (HCV) patient care have developed and expanded since the launching of highly effective direct acting antiviral (DAA) in 2013. A key issue which has been identified with HCV DAA is their potential for drug-drug interactions (DDI) with patient co-medications. An important part of the Hepatitis C care-treatment/Pharmacist assessment process (PTM) is to identify any DDI which could compromise the effectiveness of HCV treatment, either at the management of a co-morbidity, in order to carry out a DDI, where MedRec should first be completed, where there is a high probability of a DDI. Research on this process in the outpatient setting is lacking.

Aims
 • To describe the process of MedRec in an outpatient setting.
 • To measure the number, frequency, type and severity of medication interactions identified through the process of MedRec.

Methods
 A MedRec audit was conducted at an Outpatient Clinic (OPC) and the Public Health System (PHS). A random sampling of patients treated for HCV infection was taken. The process of pharmacist-led information gathering for the audit was pharmacy records using a data capture form.

The term reference was used to detect the medication that documented in the audit and that recorded during the audit were classified into specific categories of medication, using specific reference.

Results
 The term reference was used to detect the medication that documented in the audit and that recorded during the audit were classified into specific categories of medication, using specific reference.

Conclusion
 There is a need for a study to identify the prevalence and management of drug-drug interactions (DDI) in the outpatient setting. This study identifies the prevalence and management of drug-drug interactions in the outpatient setting. The study identifies the prevalence and management of drug-drug interactions in the outpatient setting.

Keywords
 Hepatitis C, Medication Reconciliation, Outpatient Clinic, Pharmacy Department, St. James's Hospital, Dublin, Ireland.

Interaction	Frequency (%)	Severity (%)
Drug-drug interaction	40.0 (70)	20.0 (30)
Medication non-adherence	21.0 (36)	10.0 (15)
Medication duplication	14.0 (24)	7.0 (10)
Medication omission	14.0 (24)	7.0 (10)
Medication substitution	14.0 (24)	7.0 (10)
Medication omission	14.0 (24)	7.0 (10)
Medication duplication	14.0 (24)	7.0 (10)
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Drug-drug interactions of high prevalence in a real world Hepatitis C treatment setting. The impact of pharmacist-led pre-treatment assessment, management and outcomes in a Hepatitis C treatment patient cohort

International Journal of Clinical Pharmacy (2019) 41:1227–1238
<https://doi.org/10.1007/s11096-019-00876-6>

RESEARCH ARTICLE

Pharmacist-led pre-treatment assessment, management and outcomes in a Hepatitis C treatment patient cohort

Miriam Coghlan^{1,2} · Aisling O'Leary³ · Gail Melanophy¹ · Colm Bergin^{2,4} · Suzanne Norris^{2,5}

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Abstract
 The aim of this study was to identify the prevalence and management of drug-drug interactions (DDI) in the outpatient setting. This study identifies the prevalence and management of drug-drug interactions in the outpatient setting.

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Drug-drug interaction	40.0 (70)	20.0 (30)
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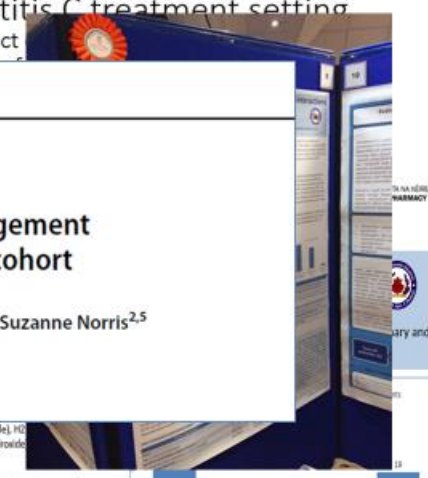
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Study 4 - A retrospective study of patients with chronic HCV infection and co-morbid epilepsy treated with DAAs

• Study Background

- AEDs are the mainstay of epilepsy treatment
- Carbamazepine and phenytoin are considered first line treatments for focal seizures
- These AEDs pose a significant DDI potential with co-medications

• Method

- Retrospective cohort study
- The process of medication reconciliation and DDI review was completed by a pharmacist for each patient.
- Time to event analysis using a matched control group

• Study population

- Patients with a co-morbid diagnosis of epilepsy, taking at least one anti-epileptic medication (AED) at baseline
- Ethical approval (St. James's & Tallaght Hospitals REC WOE40/17)

No DDI expected with any DAA regimen

- Levetiracetam
- Topiramate
- Vigabatrin
- Retigabine

Potential for significant DDI with DAA regimens

- Valproate
- Perampanel
- Lamotrigine
- Lacosamide
- Ethosuximide

Contra-indicated with all DAA regimens

- Carbamazepine
- Eslicarbazepine
- Oxcarbazepine
- Phenytoin
- Phenobarbital



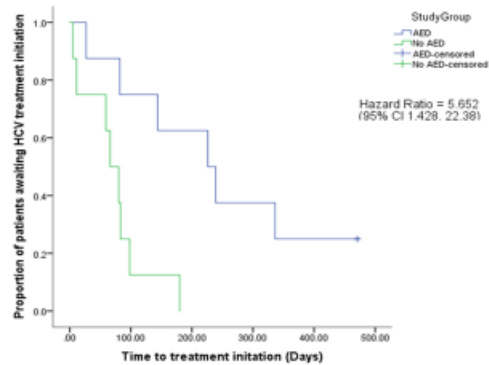
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Study 4 - Results

- Total of 22 patients recruited & AED polypharmacy was identified in 31.8% of patients
- More than one third of all AED prescriptions were subject to a potential DDI between AEDs and DAA therapy (37.5%) affecting 45.5% patients
- 75% of potential DDIs were categorised as severe
- Strategies employed to manage DDI risk included changes to AED regimens (31.8%), cessation of interacting AEDs (4.5%) and use of non-first line DAA regimens (4.5%)



Study 4 – Time to HCV treatment initiation



- AED DDI management was associated with a delay in time to HCV treatment initiation in 54% of patients as compared to the control group (Average 96 versus 50 days)
- Two complex cases: Patients unable to initiate HCV treatment
- Patients subjected to a severe potential DDI had a statistically longer timeline to HCV treatment initiation (Log rank test $p = 0.006$, HR 5.652 (95% CI 1.428, 22.379))



Study 4 – Conclusions & Implications

- **What was known prior to this study?**
 - AEDs are associated with more DDIs than any other class of medications
 - No data available on real-world management strategies of DDIs between DAAs and AEDs
- **What is the added value of this study?**
 - Study findings suggest a high rate of clinically significant DDIs between DAAs and AEDs in patients with epilepsy in a real-world setting
 - Management of DDIs is impacting on the time to initiation of HCV treatment for patients prescribed enzyme inducing AEDs including phenobarbital, carbamazepine and its derivatives
- **Implications of the new findings?**
 - A need was identified for a rapid neurology referral pathway and this is now in place



Hepatitis C Direct-Acting Anti-Viral treatment options in patients with epilepsy. A drug-drug interaction dilemma in Hepatitis C Infection.

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¹Pharmacy Department, St. James's Hospital, School of Medicine, Trinity College Dublin, ²National Centre for Pharmacovigilance, ³Department of Gastroenterology and Infectious Diseases (GIDID), Neurology Department, St. James's Hospital.

Introduction
 Epilepsy is the second most common neurological disorder worldwide after stroke and its management is primarily based on treatment with antiepileptic medications (AEMs). Patients with epilepsy and non-viral hepatitis C (HCV) infection are at risk of drug-drug interactions (DDIs) which may have a negative impact on both seizure control and HCV treatment outcome. The potential for DDIs is driven by the effect of AEMs on cytochrome P450 isoenzymes and transport proteins. Thorough assessment of potential DDIs is required prior to treatment for HCV infection, to determine their potential impact on treatment outcome and to initiate appropriate management interventions. Medication reconciliation and DDI review are processes completed as part of the 'Treatment Treatment Treatment' (TTT) initiative undertaken in our unit. There is a paucity of literature on the management of HCV DAA therapy in patients with epilepsy in a real-world setting. It should be noted that both the Scottish Intercollegiate Guidelines Network and the International League Against Epilepsy (ILAE) rate phenytoin and carbamazepine as the AEMs with the highest quality of efficacy and effectiveness data across all seizure types. However, both of these AEMs are contraindicated with all DAA regimens.

Aim
 To assess the prevalence, severity and management of potential DDIs identified in epilepsy patients controlled on AEMs with DAA-based HCV therapy as part of the TTT initiative, and the impact on time to treatment initiation.

Methods
 Patients with a confirmed diagnosis of epilepsy, taking at least one AEM at baseline who were assessed for DAA-based HCV treatment at St. James's Hospital between December 2014 and December 2015 were included in the analysis. The TTT team captured patient information pertaining to baseline characteristics and proposed HCV treatment plan through chart review. The process of medication reconciliation was completed with all patients as part of the TTT process prior to DDI assessment. The TTT team employed a standardized drug-drug interaction reference list for completion of DDI notes including the specialised University of Liverpool website, www.druginteractions.org. DDI assessment was completed for all medications listed under three descriptive categories, i.e. interaction found, potential interaction identified or potential for DDI unknown. Where a potential for DDI was identified, a narrative safety rating (S-R) was applied and a DDI management recommendation was provided. The time from initial treatment assessment to treatment initiation was measured for patients in the study group and compared with that of a matched control group of HCV treatment patients who were not prescribed AEMs.

Results
 A total of 13 patients with a diagnosis of epilepsy (4.9% of the total HCV treatment cohort) were included in this review of whom nine were male. The study identified 122 concomitant medications, of which 22 were AEMs. Table 1 below summarises:

Age group	n (%)
18-34	6 (46.2)
35-49	3 (23.1)
50-64	2 (15.4)
65-79	2 (15.4)
80-94	0 (0)
≥95	0 (0)

Sex
 Male 6 (46.2)
 Female 7 (53.8)

Age at diagnosis of epilepsy (years)
 18-24 1 (7.7)
 25-29 1 (7.7)
 30-34 1 (7.7)
 35-39 1 (7.7)
 40-44 1 (7.7)
 45-49 1 (7.7)
 50-54 1 (7.7)
 55-59 1 (7.7)
 60-64 1 (7.7)
 65-69 1 (7.7)
 70-74 1 (7.7)
 75-79 1 (7.7)
 80-84 1 (7.7)
 85-89 1 (7.7)
 90-94 1 (7.7)
 ≥95 0 (0)

Time from initial treatment assessment to treatment initiation (days)
 0-14 1 (7.7)
 15-29 1 (7.7)
 30-44 1 (7.7)
 45-59 1 (7.7)
 60-74 1 (7.7)
 75-89 1 (7.7)
 ≥90 1 (7.7)

DAA regimens prescribed included (individuals/patients):
 Sofosbuvir/daclatasvir 1/1
 Sofosbuvir/velpatasvir 1/1
 Ledipasvir/simeprevir 1/1
 Glecaprevir/pibrentasvir 1/1
 Sofosbuvir/daclatasvir 1/1
 Sofosbuvir/velpatasvir 1/1
 Ledipasvir/simeprevir 1/1
 Glecaprevir/pibrentasvir 1/1

Figure 1: AEM and DAA DDI Severity Classification

Hepatitis C Direct-Acting Anti-Viral treatment options in patients with epilepsy. A drug-drug interaction dilemma in Hepatitis C Infection.

Morris S, Coughlin M, Mahanwarthi U, O'Leary A, Singh C, Morris S, Sweeney D
¹Pharmacy Department, St. James's Hospital, School of Medicine, Trinity College Dublin, ²National Centre for Pharmacovigilance, ³Department of Gastroenterology and Infectious Diseases (GIDID), Neurology Department, St. James's Hospital, Dublin.

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 Epilepsy is the second most common neurological disorder worldwide after stroke and its management is primarily based on treatment with antiepileptic medications (AEMs). Patients with epilepsy and non-viral hepatitis C (HCV) infection are at risk of drug-drug interactions (DDIs) which may have a negative impact on both seizure control and HCV treatment outcome. The potential for DDIs is driven by the effect of AEMs on cytochrome P450 isoenzymes and transport proteins. Thorough assessment of potential DDIs is required prior to initiation of treatment for HCV infection, to determine their potential impact on treatment outcome and to initiate appropriate management interventions. Medication reconciliation and DDI review are processes completed as part of the 'Treatment Treatment Treatment' (TTT) initiative undertaken in our unit. There is a paucity of literature on the management of HCV DAA therapy in patients with epilepsy in a real-world setting.

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 Patients with a confirmed diagnosis of epilepsy, taking at least one AEM at baseline who were assessed for DAA-based HCV treatment at St. James's Hospital between December 2014 and December 2015 were included in the analysis. The TTT team captured patient information pertaining to baseline characteristics and proposed HCV treatment plan through chart review. The process of medication reconciliation was completed with all patients as part of the TTT process prior to DDI assessment. The TTT team employed a standardized drug-drug interaction reference list for completion of DDI notes including the specialised University of Liverpool website, www.druginteractions.org. DDI assessment was completed for all medications listed under three descriptive categories, i.e. interaction found, potential interaction identified or potential for DDI unknown. Where a potential for DDI was identified, a narrative safety rating (S-R) was applied and a DDI management recommendation was provided. The time from initial treatment assessment to treatment initiation was measured for patients in the study group and compared with that of a matched control group of HCV treatment patients who were not prescribed AEMs.

RESULTS
 A total of 13 patients with a diagnosis of epilepsy (4.9% of the total HCV treatment cohort) were included in this review. The study identified 122 concomitant medications, of which 22 were AEMs, resulting in 176 potential DDIs. Table 1 summarises:

DDI Management Strategy	n (%)
Interaction found	10 (5.7)
Potential interaction identified	10 (5.7)
Potential for DDI unknown	10 (5.7)

Figure 1: DDI Management Strategy

Management of these DDIs resulted in a delay in HCV treatment initiation for 50% of the epilepsy population as compared with the control group (Figure 2). This analysis however, the AEM cohort and the control group found a statistically significant difference in time to treatment initiation. The analysis to treatment initiation for epilepsy patients was longer than the control group (4.9% of cases).

CONCLUSION
 This review suggests a high rate of clinically significant DDIs between DAA and AEMs, with management of DDIs impacting on time to initiation of HCV treatment for some patients. Implementation of the TTT, with the identification and management of potentially severe DDIs to secure continued HCV treatment outcomes for this patient group. The challenge of DDIs will continue to be part of HCV treatment for patients with epilepsy in the future as newly licensed regimens display a similar pharmacokinetic profile to those prescribed in this analysis. More robust pharmacokinetic studies are needed to aid clinicians in optimising HCV treatment choice for this patient cohort.

ACKNOWLEDGEMENTS
 The authors would like to acknowledge contributions from patients and colleagues in the Pharmacy Department, GIDID Unit and the Neurology Department, St. James's Hospital.

Conclusions & implications for optimising HCV treatment outcomes

- **What was known**

- Model of care has and continues to rapidly evolve in Ireland and worldwide
- The standards and quality of care must be maintained

- **What the research has added**

The Hepatitis C Pre- Treatment Pharmacist Assessment (PTPA) - complex intervention tool designed to maintain quality of prescribing

- Regardless of treatment setting, patients must be able to engage with healthcare providers with *treatment knowledge* and *adequate resources* to ensure evaluation for & initiation on the *optimum* treatment regimen



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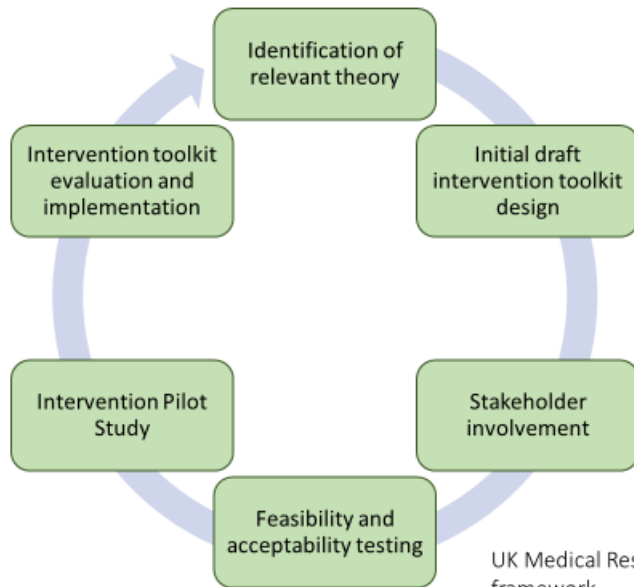
Part 2

Hepatitis C Pre-Treatment Pharmacist Complex Intervention Toolkit

“Intervention development to effect change”



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Framework for design and evaluation of complex interventions to improve health

Michelle Campbell, Ray Fitzpatrick, Andrew Haines, Ann Louise Kinnonth, Peter Sandercock, David Spiegelhalter, Peter Tyrer

BMJ 2000

UK Medical Research Council Complex intervention development framework



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Study 1 - Design, development and optimisation of the PTPA

- **Study Background**

- Positive evidence base for pharmacist-led interventions identified in part 1
- Evidence based interventions which maintain quality of care are required for devolvement of HCV treatment services

- **Study method**

- Process mapping
- Stakeholder research group formation
- Development of guiding principles for the PTPA
- Initial complex intervention design
- Development of a logic model

- **Study population:** Healthcare professionals working in the area of HCV patient care



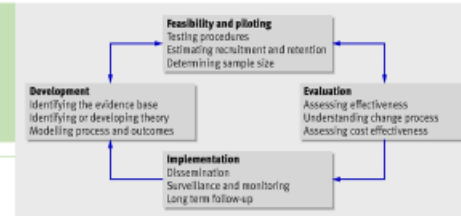
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Study 1 - Results - Guiding Principles of the PTPA

- The toolkit should capture all common & important potential points of error along the HCV treatment assessment and regimen selection pathway
- Toolkit format should flow chronologically
- The toolkit should highlight/place special emphasis on high risk patient groups. e.g. patients with cirrhosis, multiple co-morbidities and/or co-mediations
- The toolkit should help to capture and highlight any medication reconciliation or DDI issues



Study 1 - Results



- Initial draft design intervention toolkit
- Nine iterations of the PTPA intervention toolkit were reviewed by the stakeholder research group
- 35 recommendations including 29 new additions or changes
- 26 recommendations were accepted
- Stakeholder research group also facilitated assessment of toolkit user friendliness and readability in addition to face and content validity testing



Hepatitis C Pre-Treatment Pharmacist Assessment

Step 1: Patient baseline characteristics

Patient Age	YFS		Gender		
Patient Weight	kg		Date of weight		
Hepatitis C Genotype			HCV Viral Load		Date:
First Diagnosed			Route of acquisition		
Liver Disease Staging	Fibroscan: _____ kPa Date: _____		Biopsy: _____ Date: _____		Ultrasound/CT: _____ Date: _____
Co-morbidities					
Alcohol Intake					
Allergy Status					
Baseline Laboratory Markers	AST		ALT		Bilirubin
Date of Labs:	Na ⁺		Platelets		Creatinine
	Albumin		Gamma		Alpha-feto protein
			GT		
	INR		Dialysis	Y/N	Haemoglobin
Renal Function	Cockcroft & Gault				Date
Hepatitis B Markers	Core Antibody				Surface Antibody
	Surface Antigen				mIU/ml
	Hepatitis B e Antigen (if HBV infection confirmed)				HBV viral load
					e Antigen positive
					e Antigen negative
HIV Ag/Ab Combo					

Hepatitis C Pre-Treatment Pharmacist Assessment

Step 2: Staging of liver disease

Based on the available information does this patient have cirrhosis? If yes, please complete below questions		Yes	No	Not determined
If cirrhotic, has this patient had an episode(s) of hepatic decompensation?		Yes	No	Not determined
Presence or history of ascites	Yes / No	Presence or history of encephalopathy		Yes / No
Presence or history of varices	Yes / No	Presence or history of portal HTN		Yes / No
Hepatic Function Measurement in patients	Child Pugh Score	MELD Score	FIB-4 Score	
Date:				

Hepatitis C Pre-Treatment Pharmacist Assessment

Step 3: Medication reconciliation

Information sources used to determine the patient's current medications:

Patient interview	Contact with Community Pharmacy	Patient hospital medical notes
Patient's own medication list	Contact with Drug Treatment Centre	Electronic patient records
Patient's own medications	Contact with GP	Other healthcare providers
Contact with a patient carer/relative		

Source	Medication List	Potential for DDI
Community pharmacy		
Drug treatment clinic		
Hospital Outpatient Clinic		
Health food Shop /Supermarket/Gym supplements		
Online		
Illicit		
Other		
Contraception planning for both patient and partner(s)		

Hepatitis C Pre-Treatment Pharmacist Assessment

Step 4: Selection of HCV treatment regimen

HCV Genotype		HCV VL		Date	
HCV Treatment History	Treatment naïve		Treatment experienced		
Previous treatment regimens					
Previous Treatment response	Relapse	Partial response to IFN/RBV	Null responder	Viral breakthrough on treatment	
If treatment experienced with DAAs please document resistance profile					
Proposed treatment regimen					
Is ribavirin co-prescribed?	Yes		No		
Proposed treatment duration	8 weeks		12 weeks		
	24 weeks		Other:		
Does the proposed treatment regimen meet National treatment guidelines?	Yes		No		

Hepatitis C Pre-Treatment Pharmacist Assessment

Step 5: Drug-drug interaction review

Step 4: Drug-drug interaction review (See reference resource list)

Concomitant medication	Interaction potential	Action Taken	Monitoring Plan

Outcomes of MDT report discussion and plan:

CIT completed by: _____ Date: _____

Study 2 - Feasibility and acceptability of the PTPA complex intervention toolkit

- **Study Background**

- A draft version of the PTPA toolkit requires assessment of its feasibility and acceptability of use among healthcare professionals working the HCV treatment setting

- Feasibility and acceptability of the PTPA complex intervention

- **Study results**

- One of the key findings was that the toolkit was well received
- Focus group participants highlighted the following:
 - A topic guide with a specific set of research questions was developed

“The toolkit is great because it collates and disseminates this knowledge so that everyone caring for patients with HCV gets the benefit of it.”

“A great model of knowledge de-monopolisation”.

- **Study population:** Healthcare professionals working the area of HCV patient care. A purposive sample method was used to select participants
- Ethical approval (St. James’s & Tallaght Hospitals REC WOE 39/17)

- **Findings**



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Study 3 - PTPA Pilot Study

- **Study Background**
 - To test the PTPA intervention toolkit that has been developed and to identify its potential effect to determine sample size for evaluation study
- **Study method**
 - A pilot study involving four healthcare professionals.
 - Two HCPs utilised the toolkit to complete two test cases while two other HCPs completed the test cases using current standard of care
- **Study population**
 - A convenience sample of 4 HCPs were recruited to participate
- Ethical approval (St. James's & Tallaght Hospitals REC WOE 39/17)
- **Results**
 - PTPA toolkit use was associated with a 25% improvement in optimum HCV treatment regimen selection as compared with the control group
 - Expert statistical advice was sought to utilise the findings from this pilot study to confirm the sample size required for the PTPA evaluation study.



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Study 4 – PTPA Evaluation Study

- **Study Background**

- The PTPA toolkit was developed as per the MRC framework. As per MRC framework an evaluation study must be undertaken to assess the impact of the intervention developed

- **Study method**

- Matched cohort study design
- Qualitative survey to assess intervention acceptability among evaluation study participants

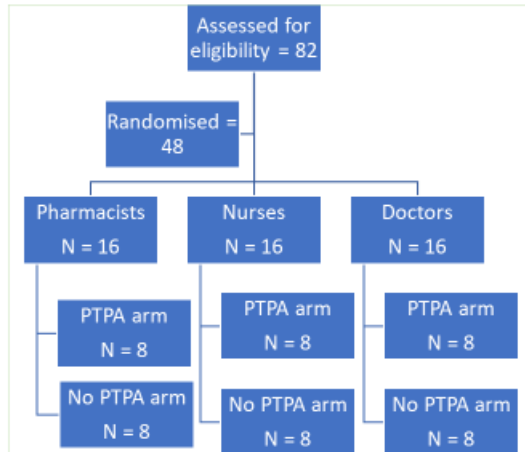
- **Study population**

- Three cohorts within this study design, one specific to each HCP grouping (N = 48)
 - Cohort 1: Pharmacists
 - Cohort 2: Clinical nurse specialists
 - Cohort 3: Consultants and registrars
- Recruitment was completed using a pre-designed study sampling frame.

- Ethical approval (St. James's & Tallaght Hospitals REC CA 2017-06)



Study 4 - Methods



- Participants were assigned to study arm by a concealed randomisation method
- Each participant had to complete 8 test patient cases
- Sample size: 58 test cases per study arm
- Outcome measures
- Participant evaluation on-line survey



Study 4 - Results

Outcome	Pharmacists	Nurses	Doctors
Selection of optimum HCV treatment	N = 16 (64 test cases per arm)	N = 14 (56 test cases per arm)	N = 15 (56 test cases per arm)
PTPA Toolkit arm	93.8% (<i>p < 0.05</i>)	76.8% (<i>p:0.28</i>)	82.1% (<i>p < 0.05</i>)
No toolkit arm	60.9%	57.1%	68.8%
DDI Detection			
PTPA Toolkit arm	61% (<i>p < 0.05</i>)	58.2% (<i>p 0.061</i>)	55.2% (<i>p < 0.05</i>)
No toolkit arm	44.9%	41.8%	46.6%
Patient interventions			
PTPA Toolkit arm	2.6 (<i>p < 0.05</i>)	2 (<i>p: 0.242</i>)	2.4 (<i>p: 0.199</i>)
No toolkit arm	1.8	0.98	1.3
Time to complete case			
PTPA Toolkit arm	20 minutes (<i>p > 0.05</i>)	19.25 minutes (<i>p<0.05</i>)	10.25 minutes (<i>p > 0.05</i>)
No toolkit arm	15 minutes	5 minutes	7 minutes

Part 2 – Conclusions & Implications

- **What was known prior to this study?**
 - Complex intervention tools facilitate healthcare professionals in making clinical decisions with prior research highlighting their positive impact on consistent patient care and positive patient outcomes
 - No previously published studies have described the design and development of a complex intervention to promote optimum HCV treatment
- **What is the added value of this study?**
 - The research process guided by the MRC framework created a function toolkit guided by the positive evidence base identified in this body of research
 - The findings of this evaluation study confirm the effectiveness of the PTPA toolkit in aiding pharmacists and doctors in selecting the optimum HCV treatment for patients
- **Implications of the new findings?**
 - This research provides a novel approach to expanding the model of care, in the field of HCV treatment
 - Represents an important contribution to the limited data surrounding complex intervention development for use in the area of HCV patient care



Pharmacist-led strategies to promote and support development and expansion of Hepatitis C treatment services

Hepatitis C Pre-Treatment Pharmacist Assessment: the development & optimisation process for a complex intervention toolkit

Coauthors: M.P. McKeown, D. O'Leary, S. A. Morris, P. D. Smith, P. D. Smith, P. D. Smith

Abstract: Hepatitis C (HCV) is a viral liver disease which poses a significant burden on the healthcare system worldwide. Over the high rates of transmission, hepatitis (HCV) and liver cirrhosis, it is a major cause of death and disability. Research is now required to identify evidence-based interventions which can improve the health of our communities at national and global levels. Pharmacist-led services in the form of patient-led self-management interventions and pharmacist-led interventions (PMIs) have been shown to be effective in the management of chronic conditions. A recent pilot study of a pharmacist-led complex intervention toolkit (PMI-CT) which incorporated self-management and patient-led interventions was conducted in a tertiary care hospital. The study identified the need for a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

Conclusion: The development of a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

Assessment of the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit

Coauthors: M.P. McKeown, D. O'Leary, S. A. Morris, P. D. Smith, P. D. Smith, P. D. Smith

Abstract: The aim of this study was to assess the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit in a tertiary care hospital. The study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

Building capacity within a Hepatitis C treatment model. The validation process for a Hepatitis C pre-treatment pharmacist assessment complex intervention toolkit.

Coauthors: M.P. McKeown, D. O'Leary, S. A. Morris, P. D. Smith, P. D. Smith, P. D. Smith

Abstract: The aim of this study was to assess the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit in a tertiary care hospital. The study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

EASL

Introduction: The aim of this study was to assess the feasibility of the Hepatitis C Pre-treatment Pharmacist Assessment complex intervention toolkit in a tertiary care hospital. The study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

Results: The study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.

Conclusions: The study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings. This study to develop a toolkit to support the development of PMI-CTs in other settings and primary care settings.



The bigger picture



- Patient outcomes
- Hospital setting
 - PTPA toolkit in use by HCV pharmacy team
 - Made available to all HCV pharmacists in Ireland
 - Electronic prescribing system medical note template developed
- National HCV Community Treatment Programme
 - PTPA toolkit incorporated into the programme for GP use
 - Phase 1 complete, phase 2 starting Jan 22nd
- Irish Pharmacy Union
 - Development of an online training programme/workshop
- Addiction Services Healthcare professionals
 - PTPA toolkit available for use



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Future Research



- Process evaluation of the complex intervention toolkit and audit of its use and outcomes in the community treatment programme
- Ongoing development of the electronic format of the PTPA intervention toolkit
- Economic evaluation of the PTPA toolkit: Micro-costing study and cost-effectiveness analysis
- Explore the potential for this type of complex intervention development process to be applied to other chronic disease states
- Explore the role and impact of pharmacist-led medication reconciliation in other outpatient settings



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