Public Health Plan for the Pharmaceutical Treatment of Hepatitis C

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An Roinn Sláinte
DEPARTMENT OF HEALTH

hi Healthy Ireland

Tús Áite do Shábháilteacht Othar
Patient Safety First

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1. Introduction

In Ireland and in other countries hepatitis C infection is recognised as a significant public health problem with its associated burden of managing and treating the disease on individuals, their families, health services, communities and society.

Hepatitis C became a notifiable disease in Ireland in 2004 and between then and 2013, 12,333 cases were notified with a peak in 2007 (n=1539). In recent years there has been a significant decrease in notifications with 847 cases notified in 2013. Studies to estimate the prevalence of chronic hepatitis C in the population have been carried out over the last few years. A study in 2009 estimated the national prevalence of chronic hepatitis C as 0.5-1.2% (20,000-50,000) while more recent information indicates prevalence is likely to be 0.5-0.7% (20,000-30,000). However although there has been a recent decrease in notifications there is still a significant burden associated with advanced stage hepatitis C infection including liver disease, liver failure, liver cancer requiring for some transplant and death.

In Ireland the main route of transmission is through sharing of needles and drug paraphernalia by people who inject drugs. In notified cases when data was available 75% of the cases of hepatitis C were in people who inject drugs. In the past transmission occurred primarily through infected blood products.

Viral eradication prevents disease progression. Until 2011 the standard treatment for people with hepatitis C infection was dual therapy interferon and ribavirin. This treatment led to a variable response but was associated with significant side effects, particularly from interferon. Recently new pharmacological treatment regimens have been developed which have demonstrated high rates of viral clearance in clinical trials. These new drug regimens are at various stages of development and regulatory approval. Some have been licensed and others are expected to be in the near future. Those licensed in the EU include sofosbuvir, daclatasvir and simeprevir. These drugs are commonly used in combination with other drugs for example Sofosbuvir +/- daclatasvir +/- ribavirin. Currently in Ireland a number of these new drug regimens are going through the assessment process for reimbursement in the HSE. Internationally there is an increasing focus on these new drug treatments. They are recognised as clinically effective treatments with significantly improved treatment outcomes and fewer side effects, however the cost of these drugs is resulting in a significant burden on health care

systems worldwide. A number of diverse strategies have been implemented by different countries to address these issues of affordability; with many adopting the approach of prioritisation based on clinical need of infected patients. Following these important developments in the area of new and emerging treatment regimens for hepatitis C, the Chief Medical Officer, in the Department of Health established a group to advise the Minister for Health through the office of the Chief Medical Officer.

The role of this advisory group was to advise on the feasibility of a multiannual public health treatment plan for patients with hepatitis C infection based on clinical prioritisation criteria for identification of patients for each treatment phase. The Advisory group included patient advocates, clinicians, the National Centre for Pharmaco-economics (NCPE), HIQA, the HSE and officials from the Department of Health and is chaired by the CMO's office (Appendix 1).

After reviewing the evidence on clinical and cost effectiveness and the budget impact of the new drug regimens, the Group advised on the development of a treatment strategy. This treatment strategy's implementation will over the next few years aim to increase the number of people with hepatitis C infection being treated effectively with complete clearance of the virus and reduce the numbers of people in the community with hepatitis C. The implementation of the treatment strategy is an important component in ultimately working towards eradication of hepatitis C in the Irish population.

2. The Scale of the Problem

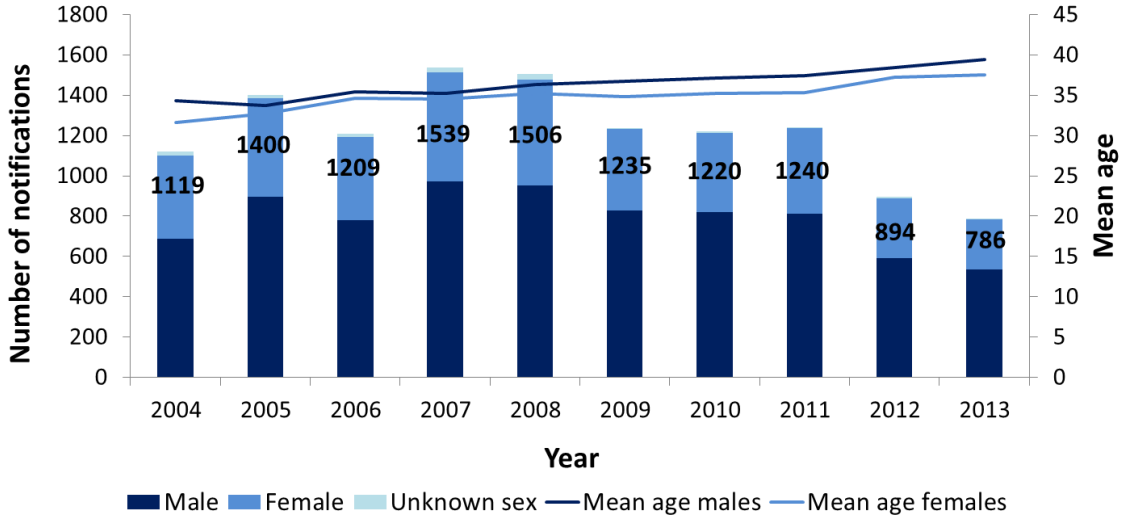
2.1 Epidemiology of hepatitis C

Hepatitis C, a small single stranded RNA virus of the *Flaviviridae* family, was first identified in 1989. There are six distinct genotypes.[(1)] Hepatitis C is a bloodborne virus which can be transmitted through equipment sharing when injecting drugs or through receipt of contaminated blood and blood products and less commonly can be transmitted occupationally, sexually and through vertical transmission from mother to child.[(1)] Worldwide, it is estimated that three to four million people are newly infected each year and that approximately 170 million people are currently chronically infected and at risk of developing liver disease, including cirrhosis and hepatocellular carcinoma (HCC).[(2)]

In 2004, hepatitis C was added to the list of notifiable diseases in Ireland. Between 2004 and 2013, 12,148 cases of hepatitis C were notified. The number of notifications peaked in 2007 (n=1539) with a marked decrease in recent years. In 2013, 786 cases were notified nationally (personal communication, Lelia Thornton, HPSC). In 2012, the case definition was altered to specifically exclude resolved cases of hepatitis C which may explain part of the reduction in the number of cases notified after this date. The trend analysis of the notification of hepatitis C by age and sex is shown in figure 1 below.

Since 2010 in Ireland, risk factor information has been available for 57% of notified cases of hepatitis C and of these, 83% were people who injected drugs. Genotypes 1 and 3 are the types most commonly seen in Ireland[(3)]. Genotype 1 traditionally has been the most difficult to treat[(4)].

Figure 1 Number of notifications of hepatitis C in Ireland 2004-2013, by sex and mean age



(Source: HPSC)

Although there were no notifications of hepatitis C prior to 2004, diagnostic data from the National Virus Reference Laboratory (NVRL) are available. Approximately 10,000 individuals were diagnosed with hepatitis C by the NVRL between 1989 and 2004. Some cases of hepatitis C that were diagnosed prior to it becoming notifiable in 2004 may have been notified since 2004, so there is potentially considerable overlap between the NVRL diagnostic data and HPSC notifications data. A study combining NVRL and HPSC notifications data, and taking this overlap account and also adjusting for undiagnosed cases, estimated the prevalence of chronic hepatitis C in Ireland at the end of 2009 to be between 0.5 and 1.2% of the population (approximately 20,000-50,000 people).[(3)] This allowed for under-diagnosis levels ranging from 50 to 80%. Evidence of lower levels of hepatitis C under-diagnosis (48%) from recent Scottish data indicate that the true prevalence in the Irish population is likely to be closer to 0.5% (approximately 20,000 people).[(5)]

However these are estimates of prevalence and the true prevalence rate in Ireland is unknown. There is no general screening of the population to determine prevalence rates with most studies only assessing the prevalence within specific risk groups. To date a national sero-prevalence study has not been undertaken.

The estimates of prevalence however do indicate that in the general population the prevalence of hepatitis C is low and most cases are from a defined risk group e.g. people who inject

drugs, people who received unscreened blood or blood products and people who were born in hepatitis C endemic countries.

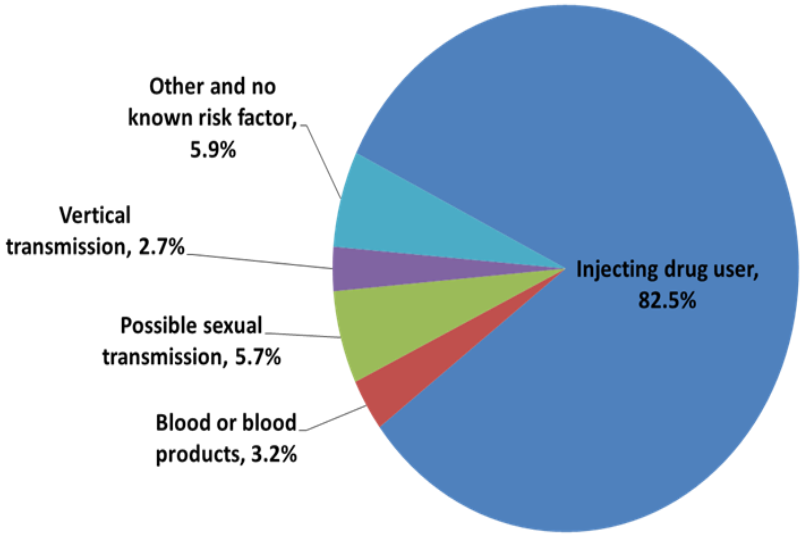
A number of studies of specific risk groups have reported various levels of hepatitis C in these groups. For example, studies of people who inject drugs (mostly heroin users) in Ireland, between 1992 and 2006 reported a hepatitis C antibody (anti-HCV) prevalence in this population of between 52-84%.[6-14] A prison study in 2011 determined that 54% of prisoners with a history of injecting heroin were anti-HCV positive and 41.5% of prisoners with a history of injecting any drugs were anti-HCV positive.[15]

A study of asylum seekers attending the Balseskin reception centre indicated that 1% of those tested under the voluntary health screening programme between 2004 and 2012 were positive for chronic HCV infection.[16]

Currently in Ireland the largest risk group for hepatitis C are people who inject drugs (PWIDs). In the past, transmission has occurred through infected blood and blood products with the majority of these infections occurring between the 1970s and the early 1990s. In 1991 routine hepatitis C screening of blood donations in Ireland commenced. Approximately 1,700 people were infected through blood and blood products in Ireland prior to the introduction of routine screening. However, as already noted the main route of transmission in Ireland was and continues to be through the sharing of needles and drug paraphernalia by people who inject drugs. Most new cases identified in Ireland are also in those who inject drugs (see figure 2 below).

There may be a significant number of undiagnosed cases of HCV in the recent migrant population in Ireland. Although asylum seekers are routinely offered infectious disease screening, there is no systematic testing for other migrants. At the time of the 2011 census, there were 766,770 non-Irish nationals living in Ireland. Based on census data on the number of people living in Ireland by country of birth (CSO unpublished data, CSO) and published data on the prevalence of anti-HCV by country of birth[17] over 10,000 of these are likely to be chronically infected with HCV (personal communication: Niamh Murphy, HPSC). This assumes that the prevalence of HCV in the migrant population in Ireland is similar to published data for the general population in their country of birth.

Figure 2 Most likely risk factor (%) for cases of hepatitis C notified 2010-2013 (where data available, n=2354, 57%)



(Source: HPSC)

2.2 Burden of Disease

Hepatitis C infection is often initially asymptomatic. However, approximately 75% of those infected fail to clear the virus and develop a chronic infection. Studies show that between 5 and 20% of those chronically infected develop cirrhosis of the liver after 20 years of infection and that in patients with cirrhosis, 1.5% to 2.5% will develop hepatocellular carcinoma (HCC) each year. Up to 80% of those with HCC will die each year.[(18)] Once cirrhosis has developed, hepatic decompensation and other potentially fatal complications can occur requiring treatment and management including possibly liver transplantation. Associated with liver transplantation are many risks including rejection but there is also a risk that if the patient is not cleared of hepatitis C their transplant will become compromised due to reinfection.

Within the public health system in Ireland there are a number of liver transplants carried out each year. The number depends on several factors including the number on the transplant waiting list and the availability of donors. Using the Hospital Inpatient Enquiry System

(HIPE) the number of transplants with a diagnosis of hepatitis C between 2005 and 2013 was 89 cases. This would average approximately 10 cases a year[1]

Figures on the number of deaths recorded with hepatitis C infection as cause of death are available from the Central Statistics Office (CSO). The accuracy of these figures is dependent on the accuracy and quality of death certification and it may be the case that there is underreporting. The number of deaths recorded on death certificates with chronic or acute hepatitis C is shown in Table1.

Table 1: Deaths due to chronic or acute hepatitis C.2007 – 2012

Year	2007	2008	2009	2010	2011	2012
Deaths[2]	**7**	**11**	**14**	**31**	**19**	**14**

Death due to specified ICD10 Codes B17.1 and B18.2 from 2007 - 2012

(Source: CSO)

Studies suggest that hepatitis C infection progresses faster in (i) males,(ii) those who are older at time of infection, (iii) people who are co-infected with HIV or hepatitis B and (iv) in those who consume high levels of alcohol.[(19, 20)] Other factors that also influence disease progression include metabolic and genetic factors.[(21)]

The clinical pathway of chronic hepatitis C infection is progression to fibrosis which if untreated can progress to cirrhosis. However the clinical course of HCV related cirrhosis is unpredictable. One study (n= 384) examining the clinical course of compensated cirrhotic patients over a 5-year period documented an annual incidence of decompensation and development of HCC of 4.4% and 2% respectively.[(22)] The 3, 5, and 10-year survival rates were 96%, 91%, and 79%, respectively. In contrast patients presenting with a decompensation event (including ascites, portal hypertensive gastrointestinal bleeding, severe bacterial infection or encephalopathy) had a poorer outlook with survival rates of 81% and

[1] Note: Data are based on inpatient and day-case discharges from publicly funded acute hospitals with a principal or additional diagnosis of ICD-10-AM B17.1 [Acute hepatitis C] or B18.2 [Chronic viral hepatitis C], and a principal or additional procedure of ICD-10-AM ACHI 90317-00 [Transplantation of liver].[1]

[2] Death due to specified ICD10 Codes B17.1 and B18.2 from 2007 - 2012

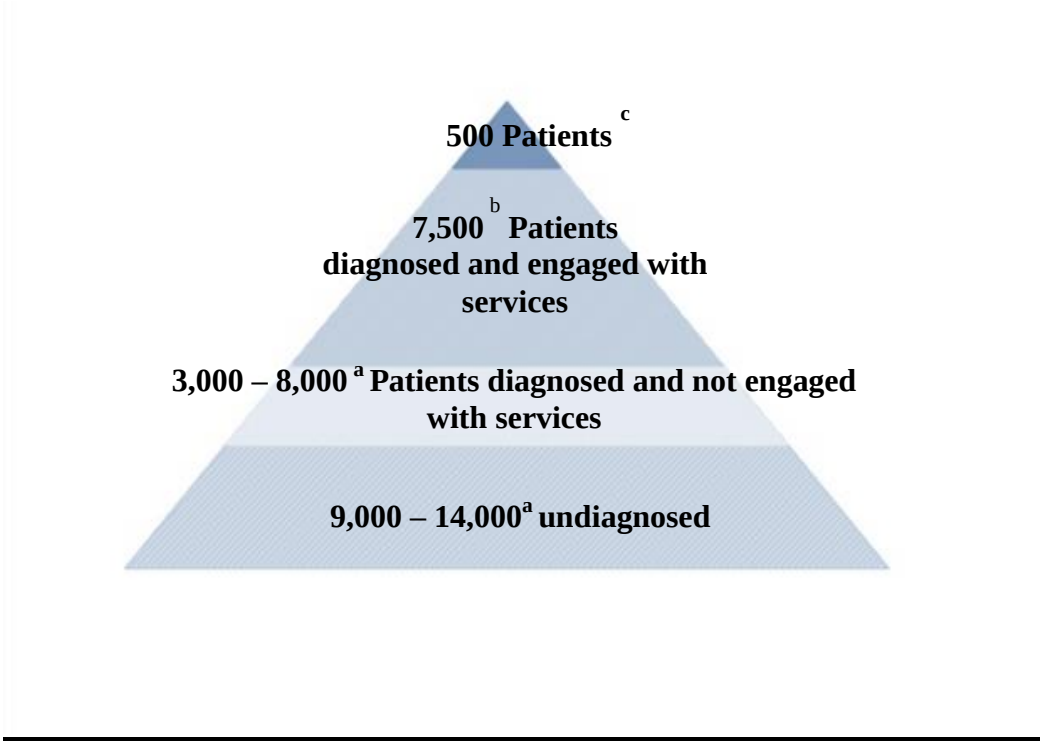
51% at 1 and 5 years. In addition the annual risk of developing HCC in this patient group was greater than 5% per annum.[23] Another study examined the natural history of patients with HCV cirrhosis.[24] The study examined the outcomes of 1050 patients (60% advanced fibrosis and 40% cirrhosis) over an 8-year period. The results clearly demonstrate that patients with a decompensation event are at highest risk of death (35% risk of death within 2 years) closely followed by patients with a Child Pugh Turcotte (CPT) score of greater than or equal to 7 on two consecutive visits (25% risk of death over 2 years). Among patients that had not decompensated platelet count correlated with decompensation events and mortality. The hepatitis C RNA level was also significantly related to clinical outcomes.

Many of the studies on the progression of hepatitis C infection are based on data from other countries. However there is some information available on the progression of hepatitis C disease in patients in Ireland and some of this data with international data can be used in modelling studies to estimate the disease progression rates in Ireland.
In estimating new cases it is important to note that the number of new cases of cirrhosis and HCC related to HCV in Ireland is dependent on the underlying prevalence, which is, as already identified somewhat uncertain.

Based on the known information of the risk factors, and the exposure of the Irish population, together with the rates of progression of disease [25, 26] it is possible to estimate the likely burden of disease. Using information from individual clinics, the National Cancer Registry of Ireland, and HIPE, together with some information on the likely prevalence and duration of disease it was possible to triangulate estimates of the expected number of cases that would be seen in coming years. Using results from this methodology it is projected that, without treatment, approximately 25-100 new HCV related cirrhosis cases and 5-25 new cases of HCC may be identified per annum.

Figure 3 below seeks to illustrate the estimated numbers of those affected by hepatitis C and their engagement or not with the health services in Ireland whilst also demonstrating how the smallest cohort at the top of the pyramid have the most complex health needs and will be the high end users of the health system. 500 patients at the top of the pyramid are the patients with the most clinical need i.e. patients that have compensated or decompensated cirrhosis, low platelets and other accelerating factors.

Figure 3: Estimated numbers in population with chronic hepatitis C



a Estimated based on NVRL data, notification data , unpublished IDVU in treatment data, Irish official statistics and worldwide prevalence levels.

b Approximate figures based on ICORN register and clinic information

c. Approximate figure based on clinical information and application of clinical prioritisation criteria.

3. Management of Patients with Hepatitis C

3.1 Prevention of Infection

Internationally strategies focus on prevention of infection through provision of information, education and harm reduction for example through provision of clean needles and drug paraphernalia. The HSE published the *"National Hepatitis C Strategy 2011- 2014".* This strategy had a number of recommendations focused on education and prevention.

Many of these strategies acknowledge that promotion of health literacy among groups at risk would be of benefit including for people who inject drugs (PWID). This information should include information on hepatitis C itself, its transmission, prevention, care and treatment options. Service providers are ideally placed to provide this information and "Health services should strengthen service providers knowledge and capacity to prevent and treat viral hepatitis in PWID" [(27)]

Additional recommendations centre on the need for meaningful engagement with stakeholders in developing the strategies to provide information to their own peer group. Peer involvement at an early stage of a PWIDs drug using career has the potential to prevent new infection, promote testing for those at risk and provide practical support and information for those considering, or undergoing treatment.

In the case of marginalised at risk groups there is a need for effective and meaning collaboration between hospitals based interventions and the specialist community/voluntary agencies, to promote optimal adherence rates and psychosocial well-being in the patient.

3.2 Screening for hepatitis C

Currently there is no universal population screening programme for hepatitis C in Ireland. However there is screening in place for patients attending services such as drug treatment services, sexual transmitted diseases services and maternity services and for specific populations for example prison services.

The prevalence of hepatitis C in the general population has not been determined although there is information, including recent information becoming available on the prevalence in different population groups.

This was evidenced by a study which was undertaken in an Emergency Department of a large city centre Dublin hospital over a 20 week period in 2014. (personal communication, Colm Bergin, HSE) The study provided an opt-out screening programme for blood borne viruses. The hospital catchment area covers some of the most deprived areas of Dublin. The screening uptake of up 70% indicates that it is feasible and acceptable to patient and staff to carry out this screening. The study findings show that for 5,299 patients screened, 287 patients were hepatitis C positive with 44 of these cases being new diagnosis. Of the patients previously known approx. 60 % were linked with the health services.

Two studies that provided universal hepatitis C screening in two large maternity hospitals in Dublin found that 0.7 -0.9% were anti-HCV positive. [28, 29] Furthermore the Irish Blood Transfusion Service found that 0.02% of new donors tested between 1997 to 2012 were anti-HCV positive (personal communication, IBTS).

In Ireland the cost effectiveness of a universal population screening programme compared to alternative strategies has not been established.

3.3 Strategies to treat Hepatitis C

The research into treatment strategies for hepatitis C suggest that treating hepatitis C is cost effective at all levels of fibrosis. Studies looking at treatment regimens with interferon, ribavirin and triple therapy would also suggest that if there are constraints on the budget that treatment with these drug regimens is most cost effective in those with advanced liver disease thus supporting the use of clinical prioritisation. [31, 32]

With the availability of these new drug treatments, research has focused on optimising treatment strategies. A recent study has shown that the total number of HCV infections is projected to decline in nearly every country studied due to a reduction in risk factors for new infections (e.g. screening of blood supply), aging of the infected population and the corresponding increase in mortality, and treatment of infected individuals.[33] However even though the total number of infected individuals is expected to decline those who remain

infected are expected to progress to more advanced stages of liver disease and thus a sharp increase in HCC, liver related deaths, decompensated cirrhosis and cirrhosis cases are anticipated. The authors suggest that the hepatitis C burden will not be controlled by the current treatment strategies and that increased treatment and /or higher efficacy therapies would be needed to keep the number of hepatitis C individuals with advanced liver disease and liver-related deaths from increasing.

Other research reviewing treatment strategies in different countries would propose that successful diagnosis and treatment of even a small number of patients can contribute significantly to a reduction in disease burden in those countries. [(34) (44)] The research would further suggest that the largest reduction in hepatitis C related morbidity and mortality occurs when increased diagnosis and treatment is combined with therapies with higher efficacy rates. This would require a significant increase in those being diagnosed and subsequently treated. This research also suggests that increased treatment and drug efficacy had most impact on morbidity and mortality when the patients being treated had more advanced fibrosis of the liver. However it also suggests that to have the largest impact on transmission of hepatitis C infection among active intravenous drug users requires treating all patients with any signs of fibrosis. To eliminate hepatitis C infection would require treating all these patients. The most effective treatment strategy was to treat those with more significant fibrosis (> F2[3]) and once that pool of patients had been depleted to expand to treat all patients including those with F0-F1. [(34)]

This research would suggest that in order to manage the existing deteriorating cohort of patients in most countries a strategy for management of the disease will require the provision of screening for undiagnosed cases parallel to the treatment of patients

3.4 The Irish Hepatitis C Outcomes Research Network (ICORN)

The Irish Hepatitis C Outcomes Research Network (ICORN) is an interdisciplinary interagency network comprising hepatologists and infectious disease consultants, virologists, epidemiologists, scientists, patient representatives, HSE, pharmacists, nurses, health economists and health technology assessment experts. This cluster of clinical and research

[3] METAVIR scoring system for liver fibrosis: F0, no fibrosis; F1, mild fibrosis; F2, moderate fibrosis ; F3, severe fibrosis; F4, cirrhosis. [(45)]

expertise overlying aim is to enhance the quality of care of patients with hepatitis C (HCV) whilst working towards and advocating for disease eradication over the coming decade – **"C it off 2025"**. The work of ICORN includes the assessment, development and evaluation of models of care, the development of clinical guidelines, the establishment of the ICORN Treatment Registry, and facilitating HCV clinical and laboratory research.

3.5 Standard Treatment Regimens

Hepatitis C treatment has evolved rapidly over the last 20 years. A cure is defined as a sustained virological response (SVR) and consists of undetectable levels of plasma hepatitis C virus RNA 12 or 24 weeks after completion of treatment.[35]

Initial clinical trials used interferon monotherapy. These were followed by the addition of ribavirin (RBV) with pegylated interferon-α (peg-IFN) which showed improved SVR rates through the 1990s and early 2000s.[36] Since the early 2000s the gold standard treatment has been a dual drug regimen consisting of a weekly injection of peg-IFN plus daily oral RBV.[37] This regimen has achieved SVR rates of 50% in genotype 1 disease and 70%-80% in other genotypes.[38]

Treatment of patients with this regimen was limited due to treatment contraindications an adverse toxicity profile and low SVR rates in patients with advanced fibrosis and prior treatment failure.[36, 39] Almost all patients treated with peg-IFN experience significant side-effects including; fatigue, flu-like symptoms, weight loss, seizures, peripheral neuropathy, bone marrow suppression and psychiatric symptoms.[37]

3.6 New Drug Regimens

In recent years new treatment agents have been developed. These directly acting anti-virals (DAAs) were initially added to the traditional peg-INF RBV regimen. Using DAAs combined with peg-INF and RBV results in improved SVR rates when compared with using peg-INF and RBV only.[37] In 2012, two first generation DAAs, bocepravir and telaprevir, were approved for use and reimbursed in Ireland in triple therapy regimens with peg-INF and RBV. Subsequently several more DAAs have become or are due to become available including; simeprevir, sofosbuvir, daclatasvir and ledipasvir.

New DAA treatment regimens which do not contain peg-INF are now available. These regimens have been shown to achieve high SVR rates in several patient groups. The Canadian Agency for Drugs and Technologies in Health have undertaken a comprehensive review of both clinical and cost effectiveness of interferon-free regimens for use in genotype 1 chronic hepatitis C.[37] Of note Genotype 1 is the main genotype among the people with hepatitis C in Ireland.

The review assessed ten relevant reports/studies. The review found that the studies reported that SVR was achieved in over 90% of patients who received sofosbuvir and ledipasvir, with or without RBV for 8, 12 or 24 weeks in treatment naïve and treatment experienced patients. SVR of over 90% was achieved in patients who received sofosbuvir and daclatasvir, with or without RBV for 12 or 24 weeks in treatment naïve and treatment experienced patients. In treatment experienced patients with cirrhosis, 100% of patients who received sofosbuvir and ledipasvir achieved SVR at 12 weeks. Lower SVR rates were seen in patients who received a sofosbuvir plus RBV regimen. Low levels of serious side effects and discontinuation were identified. This evidence suggests that high SVR rates can be attained with interferon-free DAA regimens in both treatment naïve and treatment experienced patients with genotype 1 hepatitis C. However, there were no head to head trials comparing interferon-free regimens and those that contain interferon, making it difficult to compare such regimens.[37]

3.7 Cost Impact and Affordability

The budget impact of these new interferon-free DAA regimens is considerable due to the cost of the drugs and also the size of the population to be treated.

Cost effectiveness Reviews

Ireland

In 2012, following an assessment of cost effectiveness; the NCPE recommended that two DAAs, protease inhibitors boceprevir and telaprevir were suitable for reimbursement in Ireland. These drugs were recommended for use in combination with Peg-IFN and RBV in patients with hepatitis C with genotype 1 disease. SVR rates showed improvement compared with previous treatment regimens. In 2014, the NCPE recommended the use of simeprevir as part of a triple therapy regimen with Peg-IFN and RBV for genotypes 1 and 4 in both treatment naive and treatment experienced patients. Several newer agents are in development, undergoing licensing and reimbursement decisions.

The NCPE has recently completed a report (October 2014) on the clinical and comparative effectiveness of sofosbuvir. Sofosbuvir (Sovaldi)® is licensed for all genotypes of hepatitis C. It is licensed in combination with peg-interferon and ribavirin and is the first DAA to be licensed with ribavirin alone (interferon free). The manufacturer presented many different scenarios across different genotypes stratified by cirrhosis status and previous treatment status.

The NCPE review group considered that the clinical evidence used to support the application is associated with uncertainty, in particular in patients where a greater clinical need may be identified such as cirrhotic, decompensated cirrhosis and pre-and post-transplant patients. The review group also took into account the real world data presented on previous DAAs boceprevir and telaprevir where the effectiveness was less than that reported in the clinical trials. There is insufficient data on sofosbuvir to indicate whether a similar trend will present with real world sofosbuvir data.

The cost effectiveness of sofosbuvir is influenced greatly by the presence of cirrhosis and previous treatment. In non-cirrhotic patients who have not been previously treated, sofosbuvir is not a cost effective treatment option. In non-cirrhotic patients who have previously been treated, sofosbuvir + PR may be cost effective in genotype 3 patients if given for 12 weeks only. In cirrhotic patients sofosbuvir is cost effective if given for 12 weeks however the Incremental cost-effectiveness ratio (ICER) increases above €45,000/QALY if given for 24 weeks in some scenarios.

Currently the NCPE are assessing a dossier (submitted by Janssen) for simeprevir to be used with sofosbuvir. The HTA will compare this combination with the second generation of drugs.

A further submission for daclatasvir peg-interferon and ribavirin and daclatasvir with sofosbuvir was received at the end of November 2014.

A single tablet regimen manufactured by Gilead Sciences Ltd combining sofosbuvir and ledipasvir was licensed by the European Medicines Agency in November 2014. A further interferon free regimen manufactured by Abbvie is expected to be licensed in January 2015.

In 2014 the European Union's Directorate General for Health and Consumers (SANCO) requested a summary of regional and national assessments of sofosbuvir. The summary report was created by EUnetHTA in collaboration with the Medicine Evaluation Committee (MEDEV). Ten countries (including Scotland, Germany, France, Netherlands) across Europe contributed to the report. Overall sofosbuvir was found to be effective as part of both interferon free and interferon containing multi-drug regimens. These regimens achieved high SVRs in several subgroups of hepatitis C patients including subgroups where interferon was not tolerated or contraindicated. Sofosbuvir was generally well-tolerated. While the magnitude of benefit varied considerably most countries (Spain, Scotland, Netherlands) agreed that sofosbuvir was of added value in the treatment of hepatitis C.

The cost of sofosbuvir is considerable with a 12 week course costing from €40,475 to €57,000 in the reporting countries. Despite the cost, in most countries where cost-effectiveness was taken into account, treatment regimens were judged to be cost-effective. Most countries found some or all scenarios cost effective however there were methodological issues highlighted in many of the assessments. It is difficult to assess these judgements as cost-effectiveness thresholds differ or were not explicitly defined.

Recommendations following Health Technology Assessments in Other Jurisdictions

National Institute for Health and Care Excellence (NICE) UK

NICE recommended both telaprevir and boceprevir in combination with pegylated interferon and ribavirin for use in patients with genotype 1 in April 2012.

In July 2014, NICE published an appraisal consultation document for sofosbuvir. The draft recommendation from the committee was not to recommend sofosbuvir within its marketing authorisation for treating chronic hepatitis C in adults. At that time, the committee recommended that NICE request further analyses from the manufacturer for sofosbuvir in combination with ribavirin, with or without peg-interferon alpha compared with peg-interferon alpha and ribavirin in patients with genotype 1 and 3 in preparation for the second appraisal committee meeting. Revised recommendations to the original July recommendations were published in August 2014 when a number of recommendations were made:

Sofosbuvir in combination with PR:

a) Recommended for all patients with GT1
b) Cirrhotic patients with GT3 TN
c) Non-cirrhotic GT3 patients only is treatment experienced
d) Not recommended for genotypes 4, 5 and 6

Sofosbuvir in combination with ribavirin alone:

a) Not recommended for genotypes 1, 4, 5 and 6
b) Is recommended as an option for treating genotype 2 patients only if:
    a. they are TN and intolerant to or ineligible for interferon therapy or
    b. if they are treatment experienced, regardless of interferon eligibility
c) Is recommended for patients with genotype 3 with cirrhosis'

The full appraisal document is anticipated in January 2015.

Scottish Medicines Consortium (SMC), Scotland

The SMC accepted both telaprevir and boceprevir in combination with pegylated interferon and ribavirin for use in patients with genotype 1 in 2011.

In June 2014 sofosbuvir was accepted for restricted use within NHS Scotland for genotypes 1-6. Use in treatment naïve patients with genotype 2 is restricted to those ineligible for, or are unable to tolerate peg-interferon alpha. Use of the 24 week interferon-free regimen of sofosbuvir, in combination with ribavirin, in patients with genotype 3, is restricted to those ineligible for or unable to tolerate peg-interferon alpha.

The Pharmaceutical Benefits Advisory Committee (PBAC), Australia

Tripe therapy regimens containing telaprevir or boceprevir with peg-interferon and ribavirin are recommended for restricted use in Australia by the PBAC.

In July 2014 PBAC rejected the submission for sofosbuvir for the treatment of chronic hepatitis C on the basis of unacceptably high and likely underestimated cost-effectiveness and the high and likely underestimated budgetary impact on the Pharmaceutical Benefits Scheme.

Canadian Agency for Drugs and Technologies in Health (CADTH), Canada

Telaprevir and boceprevir regimens were recommended for use only in patients with F2-F4 liver status.

CADTH has recommended that sofosbuvir be listed for the treatment of chronic hepatitis C virus infection in adult patients with compensated liver disease, including cirrhosis based on specific criteria for each genotype. The clinical criteria are as follows:

a) In genotype 1, sofosbuvir in combination with PR for patients with fibrosis stage F2-F4
b) In genotype 2 in combination with ribavirin for patients F2-F4 who are treatment-experienced or have a medical contraindication to PR
c) For genotype 3 patients in combination with RBV for patients with Stages F2-F4 and treatment-experienced and a medical contradiction to PR

There are no recommendations relating to genotypes 4-6, and a price reduction was a condition of the recommendation. In addition, it was stipulated that funding not exceed 12 weeks for the treatment of patients with genotype 1 or 2 and 24 weeks for genotype 3.

Institute for Quality and Efficiency in Healthcare (IQWiG), Germany

The process in Germany allows unrestricted use of all drugs for the first year. Assessment by IQWIG will assess whether the drug demonstrates incremental benefit over current treatment and if so the price is then agreed.

In April 2014 IQWiG published their benefit assessment for sofosbuvir based on the extent and probability of added benefit. The evaluation concluded that added benefit was not proven for genotypes 1 (& 1b), 2 (treatment naïve), 3, 4, 5 and 6. They determined that in patients with genotype 2 who were treatment experienced, an indication of added benefit (extent not proven) was apparent from the evidence.

Following a survey of European Union countries, it is clear that most countries have some form of restricted access to treatments based on prioritization criteria. This is particularly the case for the newer generation DAAs including sofosbuvir. Some European countries e.g. Poland have agreed to not reimburse sofosbuvir for any group.

The new DAAs facilitate shortened courses of treatment and are associated with higher sustained viral responses than previously achieved with relatively little toxicity. Pan genotypic licenses have been granted for some of the agents (e.g. sofosbuvir) but not for all. The regimens have been successful in patients who have previously been difficult to treat, including those with cirrhosis, HIV co-infection and those who have undergone liver transplantation. In general these agents are cost effective but the cost effectiveness varies in different genotypes and subgroups. The clinical trials to date have demonstrated response rates up to 90% and some higher. There is less data in some of these 'difficult to treat' groups and therefore observational evidence through real life use will be vital in determining whether the response rates achieved in trials will be realised in more heterogeneous populations.

USA

An economic evaluation was undertaken in the United States (US) to evaluate the cost-effectiveness of sofosbuvir plus simeprevir compared with sofosbuvir plus RBV. The patients in this analysis included subgroups of treatment naïve, treatment experienced patients, interferon intolerant and interferon ineligible with genotype 1 disease. This evaluation found that sofosbuvir plus simeprevir was more cost-effective than sofosbuvir plus RBV in the US setting.

4. Drug Reimbursement Decision Process in Ireland

4.1 Health Technology Assessment

Health technology assessment (HTA) is a multidisciplinary activity that systematically examines the safety, clinical efficacy and effectiveness, cost and cost-effectiveness, organisational implications, social consequences, legal and ethical considerations of the application of a health technology.[40] This is done in a systematic, transparent, unbiased and robust manner. Health technologies include pharmaceuticals, devices, diagnostics, procedures, care pathways and public health activities, as well as the systems within which health is protected and maintained.[41] HTA acts as a bridge between evidence and policy-making. It seeks to provide health policy-makers with accessible, useable and evidence-based information to guide their decisions about the appropriate use of technology and the efficient allocation of resources.[40]

The main issues that a HTA are concerned with are;

- Does the technology work?
- For whom does it work?
- What is the benefit to the individual?
- At what cost?
- How does it compare to alternatives?

In Ireland HTAs are undertaken by Health Information and Quality Authority (HIQA) and the National Centre for Pharmacoeconomics (NCPE). The NCPE is responsible for pharmaceutical HTAs in Ireland.

4.2 Drug reimbursement process

In Ireland once a product is licensed for use, the relevant company can make an application for reimbursement to the HSE. The HSE has statutory responsibility for decisions on pricing and reimbursement of medicinal products under the Community Drug Schemes in accordance with the provisions of the Health (Pricing and Supply of Medicinal Goods) Act 2013.[42] A reimbursement decision is made within 180 days of the application for reimbursement, subject to any necessary clock stops when additional information is sought from the company.

For a medicine to be reimbursed under the Community Drug Schemes, the supplier makes an application to the HSE under section 18 of the Health (Pricing and Supply of Medicinal Goods) Act 2013. As part of the reimbursement process the NCPE carries out an assessment and makes recommendations to the HSE. The approach includes two stages of review:

1. Rapid review of a drug which is a review of abbreviated information on efficacy, safety and budget impact. If there is uncertainty associated with any of these parameters the drug will be referred for a full assessment. This process takes 2-4 weeks.
2. Full review of the cost effectiveness dossier requires the manufacturer to submit a full dossier of the clinical and cost effectiveness for review. This process takes 90 days with a clock stop when the dossier is referred back for queries.

Products that satisfy the agreed HTA criteria used in the Irish public health system, including a cost-effectiveness threshold of €45,000 per Quality Adjusted Life Year (QALY), are normally automatically added to the Reimbursement List by the HSE.

If products do not meet the agreed HTA criteria, or uncertainty remains around clinical or cost-effectiveness evidence, the NCPE may not recommend in their favour. The NCPE can also recommend that a drug should not be reimbursed at the price quoted by the supplier.

Exceptional products which fail to satisfy the €45,000/QALY threshold may still be put forward for reimbursement subject to further with the manufacturers. The NCPE appraisal informs the discussions between the HSE and the pharmaceutical supplier aimed at securing cost effective prices for drugs. Once negotiations are complete, the HSE Drugs Group considers a range of criteria including; clinical and cost-effectiveness, budget impacts and unmet needs, and makes recommendations to the HSE Leadership on whether new products which exceed the cost-effectiveness threshold should be reimbursed. The HSE Leadership team ultimately makes the reimbursement decision.

5. Proposed Multi-annual Pharmaceutical Treatment Programme

5.1 Feasibility of a Multiannual Treatment Plan based on Clinical Prioritisation

The new and innovative Direct Acting Antiviral drugs (DAA's) provide Ireland with an opportunity to treat people with chronic hepatitis C infection effectively and consequently reduce the burden on the individuals, their families and communities and on health and social services. However although there is evidence that these drug regimens are clinically effective and cost effective, particularly for certain groups of patients with hepatitis C infection they are associated with very high pharmaceutical costs , which has a significant impact on affordability for the Irish taxpayer.

The CMO in reviewing the issue of these new effective drug regimens with a significant cost impact proposed the development of a paper for the Minister for Health to assess the feasibility of a managed multiannual approach to treatment for patients with hepatitis C. It was proposed that this approach would ensure that drug treatment for patients with hepatitis C would be provided a consistent, fair, sustainable and affordable way. By implementing such an approach resources would be used effectively and efficiently to treat and cure as many patients within a managed budget as possible. Treatment is however only one element of a strategy that contributes to an ultimate goal of eradicating hepatitis C in the Irish population.

This multiannual treatment approach should be based on good evidence of how to achieve optimal clinical outcomes for patients with hepatitis C. One of the methods suggested to optimise patient outcomes is through the use of clinical prioritisation to identify patients at greatest clinical risk. In the absence of a managed approach there is a risk that drug regimens would be prescribed on a case-by-case basis. This could result in a lack of prioritisation for treatment for patients with the highest clinical risk and that resources may not be managed effectively and efficiently. A multiannual approach allows for the projected costs of treatment to be spread out over a number of years while being based on clinical prioritisation criteria.

An assessment of the feasibility of this approach was undertaken, informed by international and national evidence and expertise. The assessment shows that a multiannual approach based on clinical prioritisation is a feasible approach to undertake in Ireland for the provision

of drug treatments for patients with hepatitis C including new and emerging DAAs (this is explored in more detail in section 5.2 below). The assessment and consultation also determined that such a treatment approach needs strong governance and management structures and robust clinical leadership and participation.

In assessing the feasibility of a multiannual treatment plan a number of areas require review. These include, which treatment strategy delivers optimum outcomes for the patient and the health system and what information is available to design the treatment programme: specifically is there information on the clinical profile of the patient population and on the strength of the clinical network.

Treatment Strategy

Should the treatment strategy be a phased strategy and if so based on what criteria?

Many health systems internationally are reviewing treatment strategies for drugs including those for hepatitis C that are very expensive and therefore pose serious capacity and affordability issues. One question is whether these health systems and services have the capacity to treat all individuals with hepatitis C in a short time frame? International experience and expertise suggests that this is a significant challenge for most health systems. To deliver such treatment in a short time frame would put significant demands on the services potentially requiring increased capacity with possible redirection of or addition of resources. A phased treatment strategy delivered over a number of years would spread the cost burden and allow for better management of resources. This would minimise any negative impact on the delivery of services and would ensure that the financing model for the treatment strategy is sustainable.

If the treatment strategy is based on phased treatment then criteria are needed to determine the treatment order. A review of international research and evidence (including modelling data) shows that strategies which take into account the stage and probability of progression of disease are likely to have a greater impact on outcomes than those which do not use this information. It also suggests that the optimum strategy depends upon the treatment regimens available and the characteristics of the population to be treated.

Therefore in Ireland a risk based phased approach is proposed which will prioritise patients based on their clinical status for treatment.

Clinical Profile of Patient Population with Chronic hepatitis C

In Ireland there is some good information, although with limitations, to allow for a clinical and risk profile of the population of patients with chronic hepatitis C to be described. This information supports a process for clinical prioritisation and phasing of treatment. As noted in Section 2 evidence and research in Ireland estimates a prevalence of chronic hepatitis C infection of between 20,000 – 30,000 people in the population. The clinical information available enables the estimation of the approximate numbers of patients who have been diagnosed and are engaged with hospital services. Clinical experts working in this field in Ireland have estimated the number of patients, from those who are actively engaged with the services, with the greatest clinical need. They have done this using information from the Irish Hepatitis C Outcomes and Research Network (ICORN) database and clinical information. This was determined using clinical prioritisation criteria based on international evidence and expertise. This process allows for an estimate of the number of patients who need treatment in the short to medium term and is useful in designing the services needed to deliver treatment. **This information will continue to be essential in designing the services for delivery of the treatment programme.**

Clinical Network

In Ireland there is a well-established clinical group that can support a national approach to clinical decisions making and the development of clinical pathways and guidelines. The ICORN treatment registry currently provides information on the clinical status and demographic profile of patients with hepatitis C infection treated with DAA treatment regimens. This Treatment Registry is an important database that can be expanded to inform the development of future clinical pathways and guidelines in Ireland.

The clinical services for hepatitis C infection are distributed across the country with eight designated centres of care in the larger hospitals in Dublin, Cork, Limerick, Kilkenny and Galway. These services can support the delivery of treatment in locations in all the major population centres and therefore will enable treatment services to be delivered to patients across Ireland.

The evidence relating to the clinical effectiveness of any new drugs will increase as they are used more commonly and in different population groups e.g. population groups with different genotypes. **In Ireland as part of the Hepatitis C Treatment Programme a Hepatitis C**

Disease Register will be developed – building on the ICORN registry. This Register will monitor outcomes for patients who are treated with new and emerging drug regimens including sustained viral clearance, side effects and patient experience. Consequently it will provide important information on the clinical effectiveness of drug regimens in the different population groups in Ireland. This Register should also include those patients who have not yet been treated.

Drug Regimens

Efficacy data for newer treatment regimens indicate that sustained viral clearances of up to 90% are achievable depending on the patient's baseline characteristics. As oral medications they are easier to take with fewer side effects and therefore more patients can tolerate the regimens with higher compliance rates.

Cost Impact and Affordability

In assessing the feasibility of a phased multiannual approach the current and future cost of drug regimens need to be taken into account. The new drug regimens are very expensive and could potentially lead to millions of euro being spent over the next few years. If there is a managed multiannual approach then this cost can be spread over a number of years. There is also opportunity within a managed approach for continued review and negotiation with pharmaceutical companies in relation to both existing drugs and also any emerging drug treatments. As part of the proposed treatment approach real world outcomes for Irish patients will continue to be collected in a Hepatitis C Register. Consequently this information will be available to inform treatment decisions both for individuals but also for groups within the hepatitis C population in Ireland. This will lead to more informed decision making on the most appropriate clinical pathways and drug treatments for patients and also inform drug reimbursement decisions.

5.2 Clinical Management of Patients with hepatitis C

To ensure that patients with the greatest clinical need are treated as a priority, patients should be assessed using clinical criteria. As a separate but important process when selecting the most appropriate and effective drug a patient's clinical profile, for example genotype and their treatment history should also be taken into account.

Proposed Clinical Prioritisation Criteria for Treatment

As noted earlier research from other countries and international experience and expertise suggests that when providing new drug treatments, DAAs, to patients with hepatitis C infection a strategy that treats those with the greatest clinical need as a priority can achieve better clinical outcomes [34] and this prioritisation is also in line with clinical guidance. [43, 44] It is suggested that this approach reduces the clinical risk for those who are at highest risk of death or irreversible damage, thus reducing morbidity, mortality and reducing the need for liver transplantation.

Internationally programmes for treating patients with chronic hepatitis C with the new DAAs for example the early access programme in the United Kingdom, have used clinical criteria to identify patients with the greatest clinical need so that they can be prioritised for treatment. Based on this international evidence and advice from clinical experts it is proposed that in Ireland the approach will be that patients with most clinical need will be prioritised for treatment with new and emerging drugs regimens. The clinical criteria used to prioritise patients for treatment will evolve over the next few years. As new drug regimens and other interventions are developed and implemented and as the disease itself evolves over time the clinical criteria will need to reflect these changes.

The clinical criteria set out for the Hepatitis C Treatment Programme should be regularly reviewed and developed by clinical experts and any changes in the clinical criteria implemented by the treatment programme.

Given the decision to apply a clinical prioritisation approach the Department of Health asked clinical experts, through ICORN, to propose the initial clinical criteria for an Irish Hepatitis C Treatment Programme. The proposed clinical criteria were to focus on those patients with greatest clinical need and particularly to focus on those patients with a risk of death or irreversible damage within the next 12 months. These clinical criteria are based on international evidence and expertise.

The proposed clinical criteria for prioritisation of patients in Ireland are as follows:

1. **Evidence of present or previous decompensated cirrhosis defined as an episode of ascites, variceal bleeding, spontaneous bacterial peritonitis or encephalopathy.**
2. **Child Pugh Score > or = 7**
3. **Patients with compensated cirrhosis and platelets <100 x 10^9/L and albumin <35 gm/dl**
4. **Non-hepatic manifestation of HCV infection likely to lead to irreversible damage within 12 months AND intolerant of or failed to respond to pegylated interferon-based treatment.**
5. **Compensated Cirrhosis outside criteria 1-4 with accelerating factors including: HIV co-infection, Genotype 1b, Viral RNA titre, hepatic steatosis.**

Any expansion or development of these clinical prioritisation criteria should be based on new evidence and information; this is examined further in section 5.3.3.

5.3 Governance and Management of a Hepatitis C Treatment Programme

The implementation of a treatment strategy that ensures the phased treatment of patients with hepatitis C based on clinical prioritisation is complex with multiple components including the development and implementation of a clinical prioritisation process; the development of a Hepatitis C Disease Register to monitor outcomes; reimbursement processes and the development of governance and management structures. Therefore it is proposed that within the HSE governance structure a National Hepatitis C Treatment Programme is established to deliver on this programme and to provide the governance and management support required to achieve the goals of optimal clinical outcomes and effective use of resources.

It is important that there is robust governance and management in relation to the implementation of the multiannual treatment programme. The HSE has the remit to provide all publicly funded health services in Ireland and therefore this treatment programme and reimbursement of the drug treatment regimens will be provided through HSE structures. The governance and management structure for this treatment programme should be in line with HSE governance structures, management processes and reimbursement decisions protocols.

5.3.1 Management Structures

The HSE should put in place a programme manager who will be responsible for the implementation of the Hepatitis C Treatment Programme. The Programme Manager will report to the Director of Primary Care. This hepatitis C programme manager will have responsibility and accountability for the delivery of all aspects of the Hepatitis C Treatment Programme.

The Role of the Hepatitis C Treatment Programme Manager includes the development and implementation of the Hepatitis C Treatment Programme including:

- Further developing and maintaining a Hepatitis C Disease Register
- Developing and overseeing the operation of clinical services to provide treatment for patients with hepatitis C
- Monitoring the performance of the services
- Developing and reporting on outcomes including patient outcomes
- Planning services including development of new services to respond to new drug treatments
- Contribute to the service planning process including preparing estimates
- Ensuring services are delivered within HSE policies specifically within reimbursement policies.

Hepatitis C Disease Register

A Hepatitis C Disease Register will be integral to the governance and management structure of the Hepatitis C Treatment Programme. A Hepatitis C Disease Register that records patient information and outcomes can be used to monitor the effectiveness of drug regimens and the treatment programme. The Register will also support call and recall system.

The Hepatitis C Disease Register variables should include:

- patient characteristics e.g. gender, age, etc.
- risk profile,
- clinical status,
- previous treatment history
- current treatment
- contraindications
- Patient outcomes

Patient outcomes following treatment will be used to develop clinical pathways and clinical guidelines. These outcomes will inform analysis of the effectiveness and cost effectiveness of drug regimens including new and emerging drug regimens and they will also be used in future strategic negotiations with the pharmaceutical suppliers.

5.3.2 Clinical Leadership

A National Operational Clinical Lead should be appointed by the HSE to provide clear clinical leadership for the programme. It is essential that there is clear clinical leadership and participation of clinicians in the Hepatitis C Treatment Programme. The Programme Manager should work with clinicians to ensure that there is good clinical input and clinical governance within the programme.

The role of the National Operational Clinical Lead includes:

- participation in the process for clinical prioritisation
- Clinical lead for the Clinical Advisory Group of the Hepatitis C Treatment Programme
- Clinical advice on the development and operation of the Hepatitis C Disease Register
- development of Quality Assurance Reports for the Hepatitis C Treatment Programme
- development of clinical pathways including the continuous review of clinical prioritisation criteria
- development of clinical guidelines and
- research

5.3.3 Clinical Advisory Group for the Hepatitis C Treatment Programme

A Clinical Advisory Group can review and provide oversight for decisions on clinical prioritisation and selection of appropriate drug treatment regimens for hepatitis C. This group can provide oversight for individual decisions or decisions about cohorts of patients.

This Clinical Advisory Group membership should at a minimum include:

- National Operational Clinical Lead for the Treatment Programme,
- representation of treating clinicians,
- independent clinical expert,
- public health and

- HSE Medicines Management Programme.

5.3.4. National Hepatitis C Treatment Programme Advisory Committee

To provide overall oversight and advice to the Hepatitis C Treatment Programme the HSE should establish a National Hepatitis C Programme Advisory Committee. This committee builds on the experience and expertise of ICORN and will be supported by the Hepatitis C Treatment Programme.

This committee advises the Hepatitis C Treatment Programme in relation to

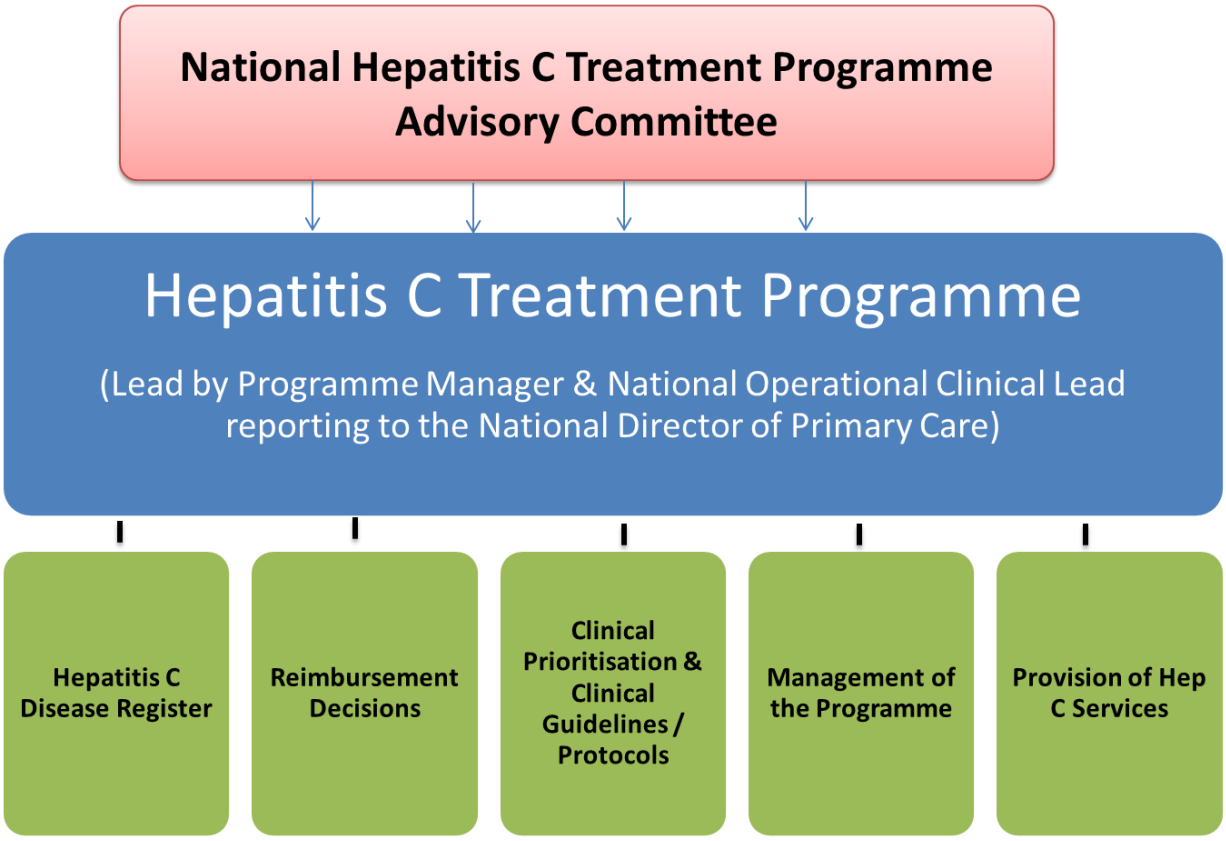
- the objectives and strategic direction of the Programme
- the overall functioning of the programme and whether it is meeting its stated objectives
- the Quality Assurance reports which will be focused on patient outcomes
- new and emerging treatments for hepatitis C
- treatment protocols, clinical pathways and guidelines

Membership should at a minimum **include:**

- Clinicians working in the treatment and management of patients with hepatitis C
- Independent clinical expertise
- Patient Representation
- Medicine Management Programme
- Public Health
- Hep C Treatment Programme Manager
- Department of Health
- National Centre for Pharmacoeconomics

The overall reporting structure of the management of the National Hepatitis C Programme is illustrated in figure 4 below:

Figure 4: Management Structure for the National Hepatitis C Programme



5.3.5 Operational Governance Process for the Provision of Drug Regimens for Treatment of Hepatitis C

The decision to provide drug treatment for patients with hepatitis C including new and emerging DAAs should have a clear decision pathway. This pathway should include a clear clinical prioritisation process, the registration of the patient on the Hepatitis C Disease Register and the HSE reimbursement process (see figure 5 below).

Clinical Prioritisation Process

Specialist Consultant Physicians and their teams will identify patients that fulfil the clinical prioritisation criteria. The team will ensure that all the relevant patient information is provided and the patient is entered onto the Hepatitis C Disease Register. (This information can be collated using information collected on a registration form (based on the ICORN registration form) and other clinical information.

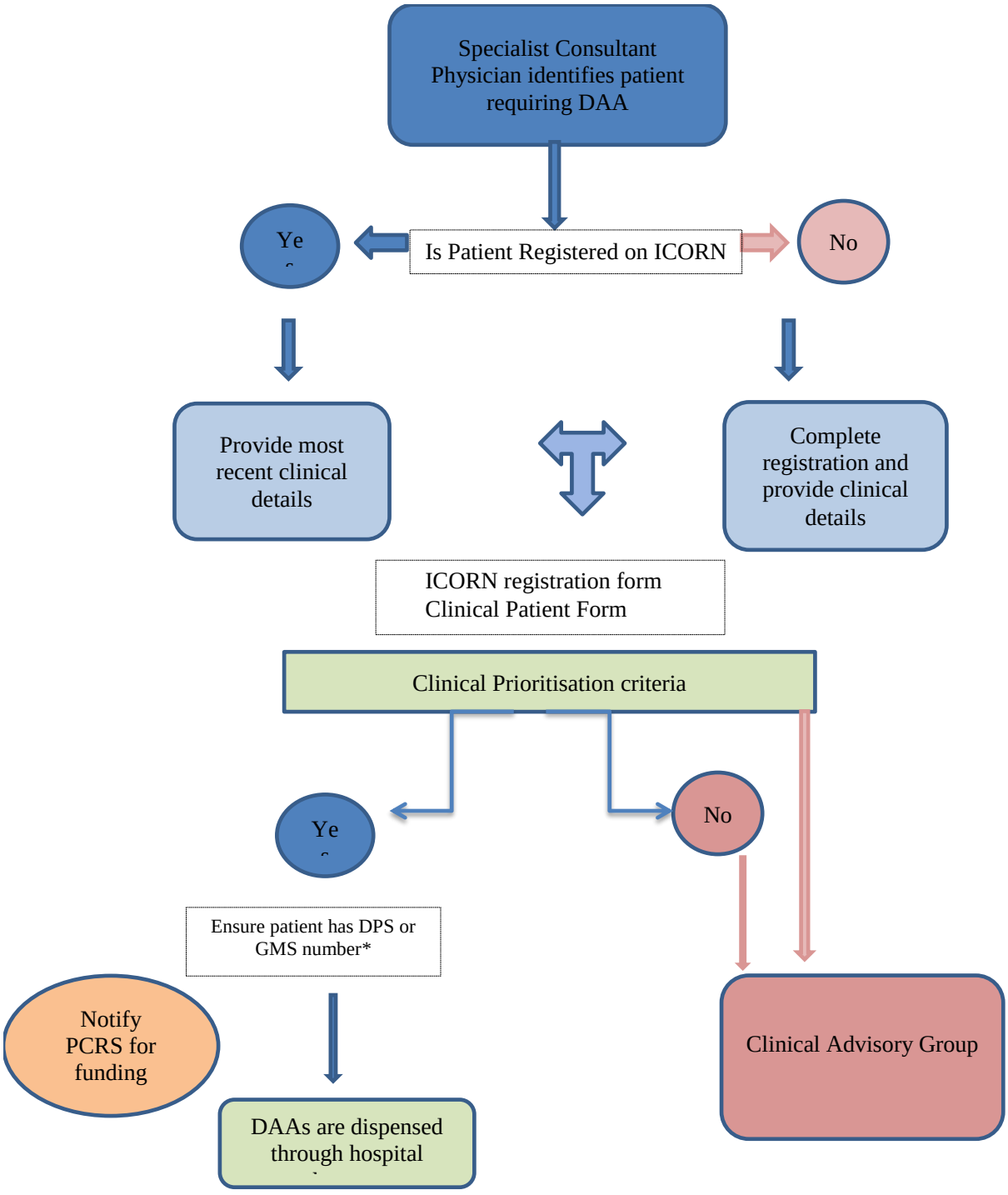
The decision process for selection of appropriate treatment regimens includes application of clinical prioritisation criteria and is also informed by the patient's clinical profile (e.g. genotype) and their treatment history.

The Clinical Advisory Group provides oversight for decisions on clinical prioritisation and selection of appropriate drug treatment regimens for hepatitis C. This group provides oversight for individual decisions or decisions about cohorts of patients.

Following the clinical prioritisation process if patients fulfil the clinical criteria then the next step involves meeting HSE reimbursement requirements. These include:

- prescription of DAAs is restricted to Specialised Consultant Physicians.
- the provision of DAAs requires pre-authorisation as per the process outlined in Diagram1
- In order for patients to be reimbursed they must have a valid GMS (Medical card) number or a DPS (Drugs Payment Scheme) number or a Health (Amendment) Act care number.
- A valid GMS. HAA or DPS number will be required for reimbursement. If this is not in place the patient should be advised to register for the appropriate scheme with the HSE.
- DAAs are currently dispensed through hospital pharmacies

Figure 5: HSE Reimbursement Pathway



6. Conclusions

In Ireland, as in other countries hepatitis C infection is a significant public health problem. There is a growing burden of disease associated with chronic hepatitis C infection for the individual patients, their families, society and the health and social services. However there are also opportunities with new and innovative drug treatments coming onto the market. There is evidence that these new drug treatments are clinically effective in trials particularly for some groups of patients with specific genotypes and there is also some early evidence that they are effective in real world treatments. As these drugs are used in treating more patients with different characteristics the evidence of their clinical effectiveness will build. It is therefore important that treatment outcomes are measured and monitored to add to this evidence base. However perhaps the greatest challenge for health systems in relation to these new drugs is their high cost.

Because of these issues the Department of Health undertook an assessment of the feasibility of a managed treatment approach – based on clinical prioritisation and phasing treatment over a number of years. This managed approach would allow for these new drugs to be provided to those with the greatest clinical need as a priority, while monitoring their clinical outcomes so as to ensure that patients receive the most clinically and cost effective drug treatment.

It was determined from the assessment that this would be a feasible approach to take as there is: a clear understanding of the clinical profile of the patients in Ireland with chronic hepatitis C infection, the presence of a good clinical network to be able to deliver the treatment and develop clinical pathways and guidelines and a treatment register already in place that can be built on to become a disease register to monitor the outcomes of patients treated with the new drug regimens. The assessment also indicated that for this treatment strategy to work it required strong governance and management structures.

It is therefore recommended that the HSE establishes a Hepatitis C Treatment Programme with a strong governance and management structure within the HSEs governance and management structures to deliver on this treatment plan.

A managed approach together with a strong governance structure will assist the HSE in negotiations with the pharmaceutical companies on the price of drugs. These negotiations

will be informed by the patient population profile, real world patient outcomes and the availability of a range of new and emerging drug treatments. The intention is to provide drug treatment to those with greatest clinical need as a priority and, dependent on cost effective drug treatments being procured by the HSE, treating as many patients as possible with the available resources. This approach will impact on the prevalence of hepatitis C in a relatively shorter period of time and will mean more patients with hepatitis C will be treated sooner. This is an important component in ultimately working towards eradication of hepatitis C in the Irish population.

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Appendix 1: Terms of Reference for the Group

Terms of Reference for the Group

- To advise on the implementation of a treatment strategy including timelines.
- To advise on the development of a treatment strategy that incorporates existing, new and emerging treatment regimes.
- To advise on the development of a Public Health Plan for the management and treatment of Hepatitis C

Appendix 2: Membership of the Group

Dr Deirdre Mulholland (Chair)	Deputy Chief Medical Officer Department of Health
Maeve O'Brien (Secretary)	Assistant Principal Officer, Cancer, Blood & Organs Policy Unit, Department of Health
Dr Roisin Adams	National Centre for Pharmacoeconomics St James's Hospital, Dublin
Prof Colm Bergin	Consultant Physician in Infectious Diseases St James's Hospital, Dublin
Teresa Cody	Principal Officer, Primary Care Unit Department of Health
Michael Conroy	Principal Officer, Cancer, Blood & Organs Policy Unit, Department of Health
Dr Diarmuid Houlihan	Consultant Hepatologist St Vincent's Hospital, Dublin
Dr Shay Keating	Medical Officer National Drug Treatment Centre
Emma-Jane Morgan	Assistant Principal Officer, Primary Care Unit Department of Health
Declan Noone	Irish Haemophilia Society
Prof Suzanne Norris	Consultant Hepatologist St James's Hospital, Dublin
Dr Lois O'Connor	Specialist Registrar in Public Health Medicine Department of Public Health, HSE East
Dr Aisling O'Leary	National Centre for Pharmacoeconomics St James's Hospital, Dublin
Brian O'Mahony	Chief Executive Irish Haemophilia Society
Nicola Perry	Community Response
Dr Mairin Ryan	Director of Health Technology Assessment Health Information & Quality Authority
Susan Scally	Principal Officer, Drugs Programmes Unit Department of Health
Michele Tait	Hepatitis C National Co-ordinator HSE
Dr Lelia Thornton	Health Protection Surveillance Centre HSE

Also Invited to Attend:

Dr. Jennifer Kiernan	National Centre for Pharmacoeconomics, St James's Hospital and Assistant Professor in Clinical Pharmacology and Therapeutics in Trinity College Dublin
Prof. Cathal Walsh	Research Leader Centre for Health Decision Science Trinity College Dublin