Cost-Utility Analysis of Direct-Acting Antiviral Agents in Treatment-Naïve Patients with Chronic Hepatitis C Virus Genotype 1 Infection

A retrospective cost-utility analysis in Norwegian setting

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Master thesis

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Abstract

Background: The new regimens for hepatitis C authorized in Norway have increased sustained virologic response, give no side effects, resulting in lower transmission rate, reduced mortality and higher quality of life for the most vulnerable categories of people. But the new treatment is also connected with extremely high costs.

Aim: To compare cost-utility of two types of treatment of treatment-naïve genotype 1 HCV mono-infected patients: newly invented direct-acting antiviral agents (DAAs) Elbasvir/Grazoprevir and Ledipasvir/Sofosbuvir with old standard treatment with Pegylated-Interferon alfa 2a/Ribavirin. The analysis will be made from payer perspective.

Methods: A Markov model was developed to simulate the disease progression with quality-adjusted life years (QALY) gains and costs per QALY as an outcome derived from treatment with DAAs over a lifetime time horizon. The target population was the treatment-naïve patients infected with chronic HCV genotype 1, baseline virus RNA ≤6 million IU/mL and absence of NS5A resistance. The primary outcome was the ICUR (incremental cost-utility ratio) for LDV/SOF and EBR/GRZ versus PEG-IFN/RBV treatment. Costs are considered from the payer perspective. The study includes deterministic analysis. Sensitivity analysis is performed to check the robustness of the model. Transition probabilities, utilities and costs were obtained from the literature. To catch the possible uncertainty of the model, a probabilistic sensitivity analysis was conducted. The expected value of perfect information (EVPI) is to be calculated. The results will be analyzed from the point of view of the budget impact analysis (BIA).
Results: The incremental cost per patient of EBR/GRZ is 786 207 NOK, cost of LDV/SOF – 920 785 NOK. The incremental effect for EBR/GRZ – 1.098 QALYs, for LDV/SOF – 1.094 QALYs. The incremental cost-utility ratio (ICUR) of 716 158 NOK – for EBR/GRZ and 841 727 NOK – for LDV/SOF per additional QALY gained basing on the old prices before rebate. EVPI and BIA demonstrated even more favorable results

Conclusion: The treatment strategies with Zepatier (GRZ/EBR) and Harvoni (LDV/SOF) are cost-effective if willingness-to-pay (WTP) threshold is assumed to be 700 000 NOK and higher. The rebated prices will improve the cost-effectiveness of new regimens. Though, additional research is still required to diminish the uncertainties of the results.

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List of abbreviations

AASLD	The American association for study of liver disease
BIA	Budget Impact Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CHC	Chronic Hepatitis C
DAA	Direct Acting Antiviral
DC	Decompensated Cirrhosis
DRG	Diagnosis-Related Group
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
EVPI	Expected Value of Perfect Information
F0	No Fibrosis
F1	Mild Fibrosis
F2	Moderate Fibrosis
F3	Severe Fibrosis
F4	Compensated Cirrhosis
GP	General Practitioner
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus

HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
HQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICUR	Incremental Cost-Utility Ratio
LIS	Drug Procurement Cooperation [Legemiddelinnkjøpssamarbeid]
LT	Liver Transplantation
LYG	Life Year Gained
MDC	Major Diagnosis Category
MEPS	Medical Expenditure Panel Survey
MSIS	Norwegian Surveillance System of Communicable Diseases
NICE	National Institute for Health and Clinical Excellence
NIPH	Norwegian Institute of Public Health
NoMA	The Norwegian Medicines Agency
pegIFN	Pegylated Interferon
PI	Protease Inhibitor
PSA	Probabilistic Sensitivity Analysis
PWID	Patients Who Inject Drugs
QALY	Quality-adjusted Life Year
QoL	Quality of Life
RAV	Resistance-Associated Variants

RBV	Ribavirin
RCT	Randomized Clinical Trial
RNA	Ribonucleic Acid
SG	Standard Gamble
SVR	Sustained Virologic Response
TTO	Time-Trade-Off
USFDA	U.S. Food and Drug Administration
VAS	Visual Analog Scale
WHO	World Health Organization
WTP	Willingness-To-Pay

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1 Introduction

Hepatitis C is a form of transmittable liver inflammation caused by the hepatitis C virus (HCV). It is difficult for the immune system to detect and eliminate the virus, and it causes chronic infection in 4 out of 5 (80%) infected. There is no vaccine against the virus. It may take many years after you have been infected until the disease is detected. Untreated chronic HCV can lead to severe consequences for health like liver cirrhosis, liver cancer (hepatocellular carcinoma) that drastically impact the life longevity and quality of life (QoL).

World Health Organization (WHO) estimates that 170 (85 million is more trustworthy by the expert opinion) million people globally are infected. [1] Thus, chronic HCV infection is a global health problem. It has been referred to as the silent epidemic that causes death, morbidity and resource utilization.

In Norway, the prevalence of HCV among adults (≥17 y.o) is approximately 0.5% that means that 20 000 – 30 000 (around 26 000), many of which have cirrhosis or are at risk of developing liver cirrhosis and liver complications shortly. The most part of the HCV patients are current or previous drug abusers and immigrants. Therefore, affecting vulnerable groups of society, the problem of chronic HCV infection receives little attention from the public. Chronic HCV infection is a big health problem in Norway with serious consequences for those who are infected as older they get, the more severe liver problems they will have. In the upcoming years the steadily growing number of people will face lower quality of life if they are not treated. It is also a big social problem as there is a high risk of transmission and the bigger number of chronically HCV infected people will lead to the higher liver-related mortality rate and significant costs associated with follow-up of the liver diseases (cirrhosis, cancer, liver transplantation). The main reason of the problem is that only a few of those infected get the treatment (5% in 2012). The lack of follow-up is reasoned also because of the demanding traditional interferon-based treatment of HCV associated with long duration, significant side effects and relatively low efficacy. For these reasons most of the infected people didn’t get the treatment.

The world health community is concerned about this problem. The WHO has set a global target to reduce the incidence of the HCV by 90% and the mortality rate by 65% to 2030 that is reflected in the “Global health sector strategy on viral hepatitis 2016-2021”. [1] The Norwegian Institute of Public Health (NIPH) has stated that, based on the infectious situation and health promotion in the country, Norway should have plans even more ambitious than

WHO sets. In 2015 a national strategy for the work on Viral Liver Infections was introduced according to which the hepatitis-related deaths and the number of new cases should be 70% reduced in Norway until 2030. [2]

In 2014 a new HCV treatment was invented and authorized in many countries, including Norway. The new generation of direct-acting antiviral (DAA) agents enabled both better lives for patients who are currently infection carriers and reduced number of new infected [3-5], which was very beneficial from the clinical point of view. Though the limitations of the new treatment included high cost, the need for sophisticated laboratory tests and trained clinicians. [6-8] For example, the costs after introducing the first antivirals (boceprevir and telaprevir) almost doubled in comparison with traditional Pegylated Interferon (pegIFN)-based therapy. Later, when other DAAs were authorized and introduced, the drug costs increased tenfold in the period of 2013-2015 (www.reseptregisteret.no). That was the main reason why the Norwegian government was forced to conduct a tender on HCV drugs in 2016. From the official sources, it is known already that the rebate for some drugs are up to 50% now. [9] According to the experts, the price reduction can lead to that more HCV infected people can be cured, so the principle of equity can be reached.

The Akershus University Hospital was one of the medical organizations in Norway that introduced new DAAs in March 2014 and shifted to the new price regime in March 2017. The high clinical effects and low side effects of the new treatment were discussed above and proved by experts, whereas economic results of the DAA-based treatment in the period of March 2014 till March 2017 (corresponding 3 years of treating HCV-infected patients with new DAAs for standard price) are absent.

The main aim of this study is to conduct cost-utility analysis of the DAA-based treatment compared with old standard treatment of chronic HCV infected patients. The study will include the retrospective analysis of the cost-effectiveness of the new interferon-free treatment compared with pegIFN-based treatment in the period from March 2014 (when new treatment was authorized) till March 2017 (when the new price regime was entered). The patient-level data was collected from the profiles of patients that were cured in Akershus in the period mentioned above. The results can motivate the decision makers to initiate the treatment of chronic HCV on all stages of liver disease (including mild fibrosis) that can lead to elimination of the prevalence, mortality related to the advanced stages of liver disease and transmission. Another positive effect in case of cost-effectiveness of the new treatment can be

that more people with disease of high priority can be treated. The positive example of Norway can be useful for the medical organizations in other countries.

Chapter 2 will explain the nature of HCV as a medical condition, its natural history, consequences for health if not treated and the interventions that are the subject of economic evaluation.

Chapter 3 presents the design and scope of the analysis. It will consist of the description of the key components of the analysis, including target population, comparators, time horizon and perspective. Moreover, a more detailed explanation of the applied analysis and theoretical framework will be given.

Chapter 4 will present the input parameters used in the model are outlined, including the resources associated with interventions, probabilities, utility and disutility weights.

Chapter 5 explains the results of the cost-effectiveness analysis that will display cost and effect for each intervention, the uncertainty of the probabilities will be checked by the number of sensitivity analysis. Furthermore, the expected value of perfect information and budget impact of the new intervention will be presented.

Chapter 6 presents the main limitations of the study and discussion part on the strengths and weaknesses of the methods and made assumptions.

Chapter 7 includes the main conclusions based on the findings of the earlier study and recommendations that relate to the DAA use and reimbursement in Norway.

Appendices contain the lists of the data used in the study, including the lists of the resources associated with interventions, utility weights and probabilities.

2 Background

2.1 Natural history of HCV infections

Hepatitis is an inflammation of the liver. The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g. alcohol, certain drugs), and autoimmune diseases can also cause hepatitis. There are five main hepatitis viruses, referred to as types A, B, C, D and E. Types B and C lead to chronic disease in hundreds of millions of people and are the most common cause of liver cirrhosis and cancer.[1]

Hepatitis C is an infectious hepatitis caused by HCV and transmitted through infected blood. In most cases the transmission goes via intravenous drug injection (91% in Norway in 2013 by the Norwegian Surveillance System of Communicable Diseases, MSIS). There is also the risk of the perinatal transmission – from infected mother to her child during the pregnancy and birth, but this rate is relatively low (4-10%). Moreover, there is a small risk of transmission by sexual or blood contact.

HCV is a small encapsulated ribonucleic acid (RNA) virus that mutates rapidly and depends on the host cell to survive and multiply. They consist of a capsule enclosing the genetic material. Six different genotypes and about 30 subtypes of the virus have been identified. The Norwegian Institute of Public Health (NIPH) admits that Genotype 1 is dominant on a worldwide basis. The genotype is important for the choice of drugs and the effect of treatment, but the course of illness is similar for all genotypes.

HCV has incubation period from 2 weeks to 6 months, whereas 80% of infected people do not develop any symptoms. It leads to that only a few are diagnosed. Following acute infection, only a small portion (15-45%) of young, healthy patients may develop a vigorous antibody and cell-mediated immune response, which leads to the spontaneous eradication of the virus [10], whereas 55-85% of those infected will develop chronic disease and face liver damage. [11, 12]

Chronic hepatitis C may lead to serious consequences for health. It involves a significant increase in the risk of liver fibrosis (four stages F0 “No fibrosis” to F4 “Compensated cirrhosis”), which in long term can lead to decompensated cirrhosis, liver cancer and liver

[1] What is Hepatitis C. WHO, 2016 (Internet) [cited October 30 2017] Available from: http://www.who.int/features/qa/76/en/

transplantation. [13] Factors that are unfavorable for fibrosis development is high age at date of infection, male sex, coinfection with hepatitis B virus and human immunodeficiency virus (HIV), excessive alcohol consumption, diabetes mellitus and non-alcoholic steatohepatitis and genotype 3 infection. [14,15] Of those with chronic HCV infection, the risk of cirrhosis is 15–30% within 20 years. [16 - 18] The risk of liver cancer (hepatocellular carcinoma, HCC) in persons with cirrhosis is approximately 2–4% per year. [19] Cirrhosis leads annually to about 170 000 deaths, whereas liver cancer caused 47 000 deaths per year in the European Union. [20] In long and severe cases, the damage to the liver is so great that the only solution is liver transplantation. It should be admitted that HCV is one of the leading causes of liver transplantation. Most often liver cancer develops in patients who have had chronic infection for over 20 years. The mortality rate among patients with liver cancer is about 4%. [21]

2.2 Epidemiology

The WHO estimates that 71 million people globally have chronic HCV infection [22]. Hepatitis C appears to be endemic in most parts of the world, although the prevalence is not evenly distributed. European and Eastern Mediterranean regions have the highest prevalence rates (2.3% and 1.5%, respectively). [23] There is considerable geographic and age variation in the incidence and prevalence of infection and of genotypes. [24, 25] The prevalence may be as high as 5% to 15% in some parts of the world, and different regions have a different risk profile and age demographics. [26]

There is a list of individuals that are highly recommended to be tested for HCV. [48] Such as: Injecting drug users; HIV positive; immigrants from high endemic areas; children born from anti-HCV positive mothers; patients with dialysis; persons that have been imprisoned, receivers of blood products before 1992 in Western Europe, North-America, Japan and Australia, and recipients of blood products any time in other than the mentioned countries. Different screening strategies have been implemented in different regions, based on the local epidemiology. Groups at higher risk of HCV infection can be identified and should be tested to prevent the transmission and the disease progress to more severe liver damage.

2.3 Testing and Treatment of HCV

The testing of chronic HCV-infection is made in both cases – to detect infection in the new patients and to test the effect of the treatment in patients that are in process of antiviral treatment. But the special attention is to be focused on the people of high risk.

There are two steps of screening and diagnosing of HCV infection. The first one is screening for anti-HCV antibodies that with serological test can identify people who have been infected with virus. In case if the test is positive for anti-HCV antibodies, a nucleic acid test for HCV ribonucleic acid (HCV-RNA test) is taken to confirm chronic infection. If negative, the test should be repeated 3-6 months after. If both HCV RNA-tests are negative, there is no chronic HCV infection, and one can assume the patient has got rid of the virus and infection-free. Further follow-up of such persons is not necessary. Those who are considered no longer infected can still tested positive for anti-HCV antibodies. [27, 28] For the patients with detected chronic HCV-infection HCV-RNA test is quantified before treatment to compare the level HCV-RNA before and after treatment to assess if virologic response is achieved. Before the treatment is initiated the HCV-genotype, IL28B genotype (strength of immune system) and liver fibrosis are evaluated as it is important for the type of the treatment, expected response and the length of the treatment.

As it was mentioned staging of HCV infection is important as it identifies patients with advanced disease, a group that requires enhanced monitoring and prioritization for treatment before the onset of decompensated cirrhosis. The stage of disease may be assessed by liver biopsy or by using a variety of non-invasive methods. METAVIR is a semi quantifying system that identifies fibroses stage via biopsy (Table 1). Though liver elastography (Transient elastography (TE) via FibroScan®) is considered as a good non-invasive alternative, liver biopsies remain the gold-standard method of assessing the extent of liver damage of patients with HCV. [29]

Table 1. Scoring Systems for Histologic Stage (Fibrosis)

Comparative Scoring Systems for Histologic Stage (Fibrosis)			
Score	IASL	Batts-Ludwig	Metavir
0	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare brifges or septae	Periportal septae (>1 septum)
3	Severe fibrosis	Numerous bridges or septae	Portal-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

Source: Cox-North P, Shuhart M. Evaluation and Staging of Liver Fibrosis. Hepatitis C Online. 2015. Available from: https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept/all

Patients with positive HCV-RNA test results made with 6-month interval are considered to develop chronic HCV. All patients with chronic HCV infection must be proposed with treatment as they are in danger to develop cirrhosis with corresponding complications and, therefore, should be treated. The aim of medical treatment of chronic HCV infection is to cure hepatitis C, prevent liver disease progression, liver cancer development, and HCV transmission.

Prioritized treatment of the patients that can transmit others is one of the prerequisites of the international target concerning epidemic control and elimination of HCV. There is an exhaustive theoretical data on cost-effectiveness of treatment of patient groups that are highly risky for spread of infection and that it will result reduced incidence and prevalence of HCV, but there is a lack of empirical evidence. Though some of the treated people can be re-infected, it is still very important to consider the transmission-preventing effect while the person is virus-free.

The most important predictor of response to treatment has been the virus genotype. Surrogate markers identify successful treatment relate to sustained virologic response (SVR) [30, 31] and is generally associated with normalization of liver enzymes and improvement or disappearance of liver necroinflammation and fibrosis in patients without cirrhosis. The infection is cured in more than 99% of patients who achieve an SVR. Patients with SVR without cirrhosis are considered treated and do not need further treatment or follow-up. Patients with severe liver disease remain at risk of life-threatening complications; however, hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. [32]

HCV was firstly identified in 1989 as the cause of all cases previously called as non-A/non-B hepatitis. In the beginning the treatment included Pegylated-interferon-α (pegIFN) only, whereas Ribavirin (RBV) was introduced much later in the end of 90s. [33] From that time till 2011 the traditional treatment of HCV in many countries, including Norway, consisted of antiviral therapy based on the use of combination of pegIFN and RBV. [34, 35] Interferon-alpha is a cytokine released by host cells in the presence of a pathogen. When administered by subcutaneous injection, it inhibited the replication of HCV and modulated the immune response against liver cells infected with HCV. [36] The addition of ribavirin (RBV), which is a nucleoside inhibitor with an unclear mechanism of action against HCV, increased cure rates. The addition of polyethylene glycol to the interferon, through a process known as pegylation, extends the half-life of interferon.

The combination of pegIFN and RBV resulted in a longer period of treatment (12 months against 6 months earlier) and higher number of patients (40% against 6% earlier) that achieve SVR. In 2001 a new pegylated interferon was used in treatment of chronic HCV. From that time the therapy consisted of pegINF/RBV led to increase of SVR rate up to 50%. [37] The problem of the traditional treatment was that it is long-lasting (24-48 weeks), gives limited likelihood of being cured, is cumbersome in use (injection), many patients face severe side effects and only small part of them can get permanent virus free.

After approval of the protease inhibitors (PIs) boceprevir and telaprevir in addition to pegIFN/RBV in 2011, SVR increased as long as the profile of unfavorable side effects and high acquisition costs. This treatment scenario has been established for both treatment-naïve and treatment-experienced patients, but only for HCV genotype 1 infection. [38-41] From 2011 till March 2014 all HCV patients in Norway were treated according to the guidelines compiled in 2011. [12], but were adjusted after authorization of telaprevir and boceprevir.

In March 2014 a new generation of pegIFN-free treatment regimens based on combination of DAAs were authorized in Norway that led to the change of the Norwegian guidelines of treatment of HCV patients in part of the patient prioritization and the drugs and drug combinations to treat. The new drugs demonstrated high curing rates (SVR≥90%), much fewer side effects, shorter treatment duration, but the costs increased significantly comparing with traditional therapy. Sofosbuvir (SOF), one of the first oral DAAs, approved by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), is nucleotide analogue inhibitor of the NS5B polymerase protein that was associated with shorter treatment courses (8-12 weeks), acceptable side effects, easy-to-register regimens, absence of resistance-associated mutations evidenced in virologic failure and pan-genotypic activity.

After 2014 new DAAs were gradually coming on the Norwegian market. According to the Norwegian Prescription Database (www.legemiddelhandboka.no), the following drugs and combinations can be currently in use: ribavirin, boceprevir, simeprevir (Olysio), daclatasvir (Daklinza), sofosbuvir (Sovaldi), ledipasvir and sofosbuvir (Harvoni), dasabuvir/ombitasvir/ paritaprevir/ritonavir (Viekirax/Exviera) and peginterferon alpha-2a. Randomized controlled trials (RCTs) have reported differences in efficacy between drugs, combinations of drugs and treatment durations, as summarized in a recent health technology assessment (HTA) report [42]. Particular DAA regimens can be effective and prescribed for particular genotype(s) independently or in combination with RBV and pegIFN.

According to the Norwegian guidelines of treatment of HCV infected adults the therapy to be chosen depends on the age, virus genotype and stage of fibrosis. The drugs that are considered as the most appropriate treatment of the HCV-infected treatment-naïve GT 1 patients are Ledipasvir/Sofosbuvir (LDV/SOF, Harvoni) and Elbasvir/Grazoprevir (EBR/GRZ, Zepatier). Both drugs are used independently once daily for 12 weeks.

The main goal of this study is to evaluate the cost-utility of two treatment approaches – the traditional pegIFN-based treatment and new DAA-based treatment, to be more precise the analysis will include the comparison of cost-utility of DAAs - LDV/SOF (with 12 weeks-therapy) and EBR/GRZ (12 weeks) – with old standard pegIFN/RBV-based therapy (48 weeks). The inputs of clinical efficacy of the drugs were derived from the available clinical trials.

LDV is available in combination with SOF and sold under the trade name "Harvoni". LDV/SOF (Harvoni©) is administrated in tablets (LDV 90 mg/SOF 400 mg). The treatment-naïve chronic HCV-infected GT 1 patients are prescribed with 1 tablet per day for 12 weeks. The drug was tested during 8 weeks with and without and 12 weeks without RBV among treatment-naïve GT 1 patients without cirrhosis. SVR rate in all three arms was between 93% and 95%. [43] In one another study of LDV/SOF SVR rate in GT 1 patients was 97% (12 weeks) and 99% (24 weeks). [44] The SVR rate among cirrhotic patients is even slightly higher. In my study I used the 95,3% (88,6%-98,7%) SVR rate for LDV/SOF 12 for non-cirrhotic and 98,6% (92,4%-100%) - for cirrhotic patients.

Elbasvir/grazoprevir (EBR/GZR), under the trade name Zepatier©, is a single oral fixed-dose combination (FDC) tablet taken once daily for 12 weeks. Zepatier is administrated in pills with dosage EBR (protease inhibitor NS3/4A) 50 mg and GRZ (protease inhibitor NS5A) 100 mg. This submission considers EBR/GZR for use in patients diagnosed with HCV GT1 (1a and 1b) or GT4 infections, irrespective of treatment experience or cirrhosis stage. Therefore, EBR/GZR is expected to displace a level of use for those technologies, previously recommended by National Institute for Health and Clinical Excellence (NICE), relevant to the GT (subtypes) considered within this submission.

The efficacy (SVR12) and safety of EBR/GZR has been evaluated in eight clinical trials. This consists of five phase III, one phase II/III, and two phase II trials, in which patients were randomized (n=7 trials) to receive EBR/GZR for 12 weeks. The pooled SVR12 results demonstrate that EBR/GZR is a highly efficacious treatment option for all patient groups irrespective of treatment experience or cirrhosis state. [45] For example, one of the clinical trials which outcome measures were used for analysis was C-Edge Co-Star. The efficacy rate

was based on the percentage of patients achieving SVR12 after study therapy. According to the results, in 95.5% (91.5 to 97.9, CI 95%) of patients SVR12 was achieved. [96] The SVR rate of EBR/GRZ among treatment-naïve patients with/without cirrhosis used in the study is 98% (0.962-0.991) that is an average among the efficacy rates derived from the available clinical trials.

The efficacy of the pegIFN/RBV in patients with genotype 1 is lower than in patients with another genotypes of HCV infection. The SVR rate of pegIFN/RBV is assumed to be 47% (42.3 – 51.7) in population of patients observed.

2.4 HCV in the Norwegian health care system

According to the official sources the prevalence of anti-HCV among adults in Norway is around 0.5% [46], still the highest among those born in the fifties and sixties (1.6%) and lowest among those born before 1940 (<0.2%). This means that officially there are an estimated 26 000 - 28 000 people in Norway who have been infected with the hepatitis C virus. In the study by Tollefsen et al., the official prevalence of chronic HCV can be overestimated, as about 40% of infected people are not diagnosed. It may be also assumed that the prevalence is too high and that the actual number of infected patients is around 16 500 people. [47] Moreover, the Norwegian Health Institute reported that around 11 000 – 17 000 people are HCV-infected and may need treatment. [48] In the treatment guidelines of hepatitis C from March 2014, it is stated that the number of people with chronic hepatitis C is about 20 000. [49] Around 83% of new cases of HCV reported by MSIS (Norwegian Surveillance System for Communicable Diseases) were reported to be infected by injection. In Norway those who are infected are mainly current or previously injecting drug users and immigrants, and the disease therefore receives little attention from the public [46], but all persons with such experience should be investigated. According to the NIPH around 41% of HCV cases are represented by the genotype 3, 44% - genotype 1, the rest – by genotypes 2,4, 5, 6. [50] Genotype 3 is the most difficult genotype to treat in Norway. Genotypes 2 and 3 are the most commonly seen among drug users.

All confirmed positive anti-HCV and/or HCV-RNA (hepatitis C virus ribonucleic acid) are reported to be registered by the Norwegian Surveillance System for Communicable Diseases (MSIS), run by the National Institute of Public Health. In MSIS, it is not distinguished between newly infected and cases previously infected, but first discovered afterwards. Therefore, all cases reported are not cases of newly infected. There are no exact figures on how

many people are infected with hepatitis C in Norway each year. The number of cirrhotic patients is around 134 per million of residents [51] or around 680 per year, 68% of the new cirrhosis cases are caused by HCV in Norway. Liver cancer is quite rare in Norway, around 215 new cases in 2012 (Kreftregisteret, 2012) where 32% of cases are caused by HCV. [52] Chronic HCV-infection is of the causes of liver transplantation in Norway. [21] Liver transplantation is considered the only proposed treatment of the decompensated cirrhosis and/or liver cancer. [53] Though the HCV-infected patients with decompensated cirrhosis are treated in Norway in case of a high life expectancy. Muhlberger et al. estimate that HCV is the cause of death of 150 cases in Norway in 2002. 35% of these cases are cause by liver cancer, and 60% - by cirrhosis, whereas HCV caused 35% of the cirrhosis-deaths and 32% of liver cancer deaths in 2002. [52]

The problem of HCV in Norway is that only 1 from 5 (20%) of chronically HCV infected could get the primary help or the specialist assistance during 2012, and even less got the drug treatment (5%). And many of those who get the drug treatment terminate the therapy at early stages of treatment and don't achieve SVR. In the light of all existing difficulties related to HCV the National Institute of Public Health of Norway has set a national strategy for the work on Viral Liver Infections that is planned to lead to the elimination of the hepatitis-related mortality and transmission until 2030.

From 1 January 2016, the regional health authorities should cover the cost of new medicines for the treatment of HCV. The costs were previously covered by the National Insurance Scheme on blue prescription (blå resept)[2]. It is, therefore, the responsibility of the Regional Health Authorities to assess resource and treatment outcomes for this patient group against other needs in accordance with current prioritization criteria and financial framework.

Drug Procurement Cooperation or Legemiddelinnkjøpssamarbeid (LIS) [on Norwegian] formed by the health regional authorities from the members of the Norwegian Association for Infection Medicine, the Norwegian Society for Medical Microbiology and the Norwegian Gastroenterological Association aims to lay the foundation for the agreements on the purchase and delivery of the drugs, thereby reducing the costs of the patient care. The Managing Directors of the health regional authorities use the recommendations of LIS HCV specialist group as the main instructions in all health care activities related to HCV.

The situation with HCV in Norway changed a lot for the last five years. Many new drugs emerged and were authorized in Norway, so almost all chronically infected patients can be

[2] If you have a serious illness, the state can partially cover expenses for pharmaceuticals, food and medical supplies on blue prescription. There are also other arrangements to get covered parts of your expenses if you have large expenses. https://helsenorge.no/legemidler/blaresept

cured. Nevertheless, the high costs associated with new treatment and limited health care budget forced to follow the politics of prioritization, when the treatment can be reimbursed only for a particular category of patients with the most cost-efficient treatment option among all available on the Norwegian market. For this purpose, the general rules or guidelines for management, follow-up and treatment of chronically HCV-infected patients in Norway were submitted by the working group of the clinical experts from the number of LIS. The first version of the guidelines was published in 2014 and updated in 2017. According to these guidelines the group of HCV-infected patients should get the treatment considering efficiency, safety and price.

Therefore, all decisions concerning the allocation of national insurance resources are made basing on economic evaluation of the treatment alternatives. Those money are distributed among the treatment technologies and patient groups within the Norwegian healthcare sector. Any new drug or treatment technology cannot be authorized for usage in Norway without being analyzed from the point of view of its cost-effectiveness. Cost-effectiveness analysis (CEA) is undertaken as a part of the allocation decision process for the new drugs.

2.5 Existing economic evaluations of HCV treatment

The clinical efficacy of new pegIFN/RBV-free regimens – potential anti-HCV treatment options - should be proved by studies and clinical trials to be authorized in Norway. As long as new drugs are available in clinical use, their effectiveness for the real world setting and impact on health-related quality of life is required to be assessed in frames of the economic studies. The CEA of the new IFN-free regimens for chronic HCV were made in USA and many European countries confirming the cost-effectiveness of most of the new DAAs for the chronically HCV infected patients.

In recent years the cost-effectiveness of Ledipasvir/Sofosbuvir in treating genotype 1 HCV infected patients was shown in some studies. [54-56] In the study by Younussi et al., the double therapy of SOF/LDV demonstrated the optimal short- and long-term health and economic outcomes compared with other currently used therapies across treatment- naïve and -experienced patients with different stages of fibrosis. For example, the usage LDV/SOF in treatment-naïve genotype 1 HCV infected patients resulted the lowest incidence of DC, HCC, liver transplantation and HCV-related deaths in a long-term perspective.

There is still a limited number of studies devoted to the cost-effectiveness of Elbasvir/Grazoprevir since it was authorized recently (in 2017 in most countries), but some studies have already shown its high cost-effectiveness especially in genotype 1a HCV infected patients. [57] In the study of Corman S et al., EBR/GRZ was economically dominant regimen in comparison with other DAAs, including LDV/SOF, for treating Genotype 1a non-cirrhotic and 1b cirrhotic HCV infected patients. It was cost saving in all other subpopulations.

The recent study by Wisløff T. et al. was devoted to the cost-utility analysis of all DAAs authorized in Norway and in active use in treatment of chronic HCV infection. The economic comparison was made for genotypes 1, 2 and 3 as the most prevalent in Norway. The analysis did not include EBR/GRZ as it was not still authorized at that moment. In that analysis the Markov model for people who inject drugs (PWID) was used as this category of patients gives the highest prevalence. The 12-week treatment with LDV/SOF was found as the most cost-effective option for PWID among other DAAs in Norway. [58]

But still there is a lack of sufficient assessment of the long-term clinical and economic impact of LDV/SOF and, especially, newly authorized EBR/GRZ in different subpopulations in Norwegian perspective.

3 Methods and materials

3.1 Comparators

The main aim of this study is to evaluate cost-effectiveness of DAA-based treatment of HCV infected treatment-naïve Genotype 1 patients compared with old standard therapy consisting of pegIFN/RBV. As it was mentioned above the comparison will be based on the patient-level data provided by Akershus University Hospital. Patient-level data includes the information of initial tests, therapy prescribed and the treatment result (achieved or non-achieved SVR). Three treatment scenarios were compared by modelling the process of treatment and disease progress of one cohort of 1000 patients: first model describes 12-week treatment process with EBR/GRZ, second model –12-weeks therapy with LDV/SOF and third model – 48-weeks treatment with pegIFN/RBV. The focus of the study is on period from March 2014 till March 2017 when the first DAAs were introduced in Norway and provided by producers for wholesale without rebates. Both new drugs LDV/SOF and EBR/GRZ are authorized in Norway and were compared within CEA by a very few studies.

3.2 Population

To accurately simulate treatment schedules and outcomes, the main characteristics of the patients should be identified as it influence the treatment selection and sometimes the disease progression. Among the characteristics that matter for the therapy to be chosen: cirrhosis status, HCV genotype, treatment history (treatment-naïve or treatment-experienced), presence of baseline NS5A resistance-associated variants (RAV) for Genotype 1a and baseline HCV RNA level (≤6 million or ≥6 million IU/mL) for treatment-naïve patients. The study includes the treatment-naïve cirrhotic and non-cirrhotic HCV-infected patients with genotype 1 with baseline HCV RNA level ≤6 million IU/mL. Patients with genotype 1a and 1b are not divided, therefore presence of baseline NS5A RAV for Genotype 1a was not considered. The study includes age-based all-cause mortality rate based on data from Statistics Norway.

Until March 2017 the principles of prioritization of patients were applied in HCV treatment. The decision to treat an individual patient were to be taken based on knowledge about the duration of the infection, inflammation rate, fibrosis stage, and genotype and thus the

likelihood of successful treatment. Additionally, the incidence of risk factors associated with increased likelihood of progression of fibrosis should be considered. [49] Cirrhosis develops only at 1/3 of the chronic HCV infected patients, meaning that most of the patients with absence or mild fibrosis have a good prognosis to get rid of the virus without treatment.

In the model I considered the fibrosis stage and included the data on the patients who fit the requirements of the national guidelines according to which "all treatment-naïve and treatment-experienced patients with significant fibrosis (METAVIR ≥ F2 or LSM ≥ 7kPa), compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, must be considered for therapy. Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities". Thus, all patients entering the model had the liver stiffness cut off value at the level of ≥7 kPa that corresponds moderate/advanced fibrosis or compensated cirrhosis (F2, F3 and F4).

The baseline characteristics of the patient-level data provided needed for the model are the following:

1) The number of GT1 HCV infected patients is 121 that were treated in the period March 2014 – March 2017.
2) The number of patients by the fibrosis stage based on the Fibroscan classification [59]: 79 patients with METAVIR F2 (Fibroscan ≥7kPa), 18 – with F3 (≥10 kPa), 24 – METAVIR F4, compensated cirrhosis (≥13kPa).

As it is widely known the drug users are most often carriers of the HCV and the model should consider the details about patients who inject drugs (PWID). It is assumed that when the therapy is initiated, all patients enter the model without status of alcoholics and drug abusers. All former drug abusers are passing drug assisted rehabilitation (in Norwegian: Legemiddelassistert Rehabilitering) and their life expectancy is similar to the general public. Thus, such risk factors like alcohol consumption and drug addiction were excluded. Otherwise, it would require additional model with different transition probabilities and mortality rates. Presumably, dynamic model could catch all the risk factors in the specific patient population.

3.3 Model overview

In the analysis I used a Markov cohort state-transition model to assess the economic benefit of the DAA-based treatment with LDV/SOF and EBR/GRZ separately vs. old standard pegIFN-based therapy in patients with HCV GT1 in Norway from the payer perspective.

The study includes three models corresponding the therapies to be compared – LDV/SOF, EBR/GRZ vs. PEG-IFN. To make the results more representative, I used one cohort of 1000 patients for each treatment strategy where 650 patients entered the model with diagnosed fibrosis METAVIR stage F2, 150 – with moderate fibrosis stage F3, and 200 patients – with compensated cirrhosis, fibrosis METAVIR stage F4. The proportion used in the model partly corresponds the proportion of the patient level data (~65% of patients at stage F2, ~15% - at stage F3, ~20% - at stage F4). Moreover, the number of 1000 patients equal the number of HCV infected patients cured in Norway annually, so it is curious to evaluate the long-term health outcomes and costs of HCV treatment, though only genotype 1 HCV infected patient group was analyzed. [50]

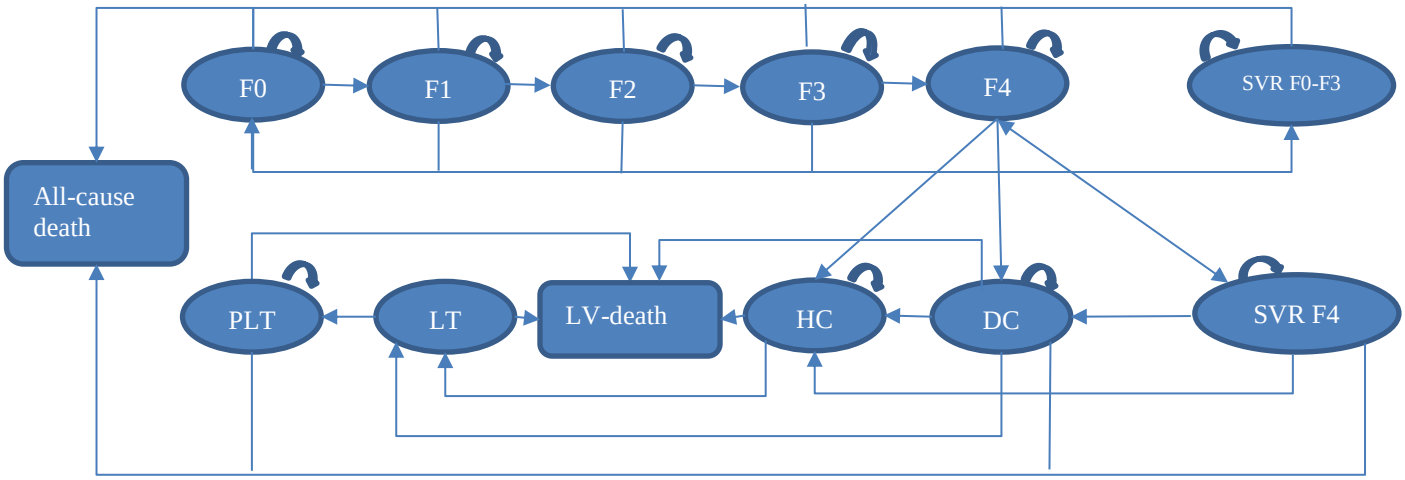
The model simulates the natural history of chronic HCV infection by means of health states reflecting the progression of the liver disease in patients that achieve or do not achieve SVR during the prescribed therapy with DAAs or old standard treatment.

The main conceptualization of the model of chronic HCV was made by the NICE committee that was used in this study.

The model includes 13 health states using transition probabilities that reflect the progression or regression of the disease. The transition probabilities were taken from the literature and published cost-effectiveness models and reflect the probabilities of non-treatment transitioning from one health state to more severe stages.

The Figure 1 illustrates the state-transition Markov model. The structure of the model was designed to show the progression of the chronic HCV infection based on the relevant literature. A lifetime horizon (75 years) was applied with one-year cycle, and the patient can be only at one health state per cycle. The circles represent health states and the squares represent the events (death in this model).

Figure 1 State transition diagram for chronic HCV and liver disease model (treatment with DAAs)



The model consists of the following health states: No fibrosis (F0), Portal fibrosis without septa (F1), portal fibrosis with new septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), liver cancer or hepatocellular carcinoma (HCC), Liver transplant (LT), post-liver transplant or subsequent years (PLT), liver-related death (LV-death), death from all other causes (All-cause death), sustained virologic response (SVR).

Hepatic fibrosis stage is based on METAVIR fibrosis scoring system. The health states F0- correspond no fibrosis, F1 – mild fibrosis, F2– moderate fibrosis, F3 – advanced fibrosis, F4 – compensated cirrhosis, DC – compensated cirrhosis, HCC – liver cancer, LT – liver transplantation, PLT – post-liver transplantation, LV-Death – liver-related death. The more detailed clinical information about health states can be found in section 2.3. Additionally, the "All-cause death" was put in the model corresponding the background mortality.

The patient enters the model at the initiation of the treatment, receiving pegIFN/RBV, LDV/SOF or EBR/GRZ, described by a state-transition model to show the outcomes in the life-time horizon. The patients enter the model at a fibrosis METAVIR stage (from F2 to F4) and may progress to subsequent stages of liver disease, achieve SVR (get rid of the infection) if treatment is successful, can stay in the same health state or die. Without successful treatment the transition to less severe stages is not possible. SVR is considered a cure for all non-cirrhotic patients that have no risk of reactivation of HCV infection. SVR 12 was defined as HCV RNA≤15 IU/mL and assessed 12 weeks after the completion of the therapy. Patients, that have achieved SVR, are assumed to have a life expectancy equivalent to the general population. The transition probabilities are based on the data from the literature, considering opinion of clinical experts, and statistical data (all-cause death).

The model includes some assumptions that were based on the opinion of the clinical experts with expertise in treating HCV. All assumptions used in the model are consistent with previous HCV NICE submissions.

Since the likelihood that the chronically infected person can spontaneously clear of HCV is small, this health state is not included in the model. There is a risk of reinfection and the person after achieving SVR can return to the previous health state corresponding a stage of fibrosis the patient entered the model (from SVR F0-F3 to F0-F3 or SVR F4 to F4). The patients with cirrhosis after achieving SVR F4 are still at risk of progression to DC or liver cancer - HCC. [72] For this purpose, SVR state was stratified by patient's baseline fibrosis stage before treatment ("SVR, F0-F3" and "SVR, F4"). Patients who return to the chronic HCV health states can develop serious liver disease. If the patient is diagnosed with decompensated cirrhosis or liver cancer, liver transplant can be the only treatment option. The liver-related mortality is considered if the person has DC, liver cancer or transplanted. Liver-related death is attributed to liver failure or liver-related complications (DC, HCC, LT, PLT), excluding other common causes of death. The liver-related death probabilities were taken from the literature.

The age-based background mortality was considered in all health states in the model excepting liver cancer and LT as in these states the patient is supposed to be hospitalized and the likelihood of the background mortality is small. The important task was also to reflect the time-dependency of all-cause death probabilities. I assumed that probability of death changed every 10 years in the model and, therefore, added seven additional groups of death probabilities reflecting 75-year horizon. "All-cause death" and "Liver-related death" are absorbing states, meaning that there are no transition outwards from these states.

The patients that achieve DC or HCC can undergo liver transplant (LT) and those who survive after LT shift to post-LT stage with probability of liver-related death that is still higher than of the general population. I assume that LT is the only treatment option for those with DC and liver cancer, disregarding DAA-based treatment. This assumption has "pros" and "cons" in the national and international guidelines. From one side, the American association for study of liver disease (AASLD) and Infectious Diseases Society of America (IDSA) guidelines based on the clinical trial admit that the patients with DC who receive the DAA therapy can experience improvement in clinical indicators of the liver disease [60-63], however these indicators can be insufficient to avoid liver-related death or need for liver transplantation [64], that means that not everybody can benefit from the antiviral therapy. From another side, the Norwegian professional guidelines on treatment of hepatitis C, insist that the patients with DC can be

offered with antiviral therapy (Daily-fixed dose combination of LDV/SOF (90/400 mg) with low initial dose of ribavirin (600 mg)) and should be guided by hospital departments who have experience of treatment of this patient group, but still the advanced stages of liver disease like DC is supposed to have different consequences, including high probability of HCC, LT and LV-death. For this reason, the annual transition probabilities from compensated cirrhosis to decompensated cirrhosis or liver cancer were based on the natural history of chronic HCV derived from the literature. [57]

The model assumed time-independent disease transition probabilities meaning that probability of moving between stages is independent of the time in the earlier mild state. [83]

The probability to be cured (virus-free) after treatment completed is based on the SVR (or effectiveness) rate of a drug, which can be found in the literature or clinical trials. Thus, in analysis I used SVR rate of EBR/GRZ, LDV/SOF and PEG-IFN to calculate the transition probability from F0-F3 to SVRF0-F3 and from F4 to SVRF4, corresponding the successful treatment. Equation used for converting rates into probabilities and vice versa is as follows, where *p* is the probability, *r* is the rate, and *t* is the period:

$$p = 1 - \exp(-r * t), \quad (1)$$

According to NICE, the SVR rate for therapy with EBR/GZR for GT1a TN NC patients is around 0.98 (0.962-0.991) based on the result of network meta-analyses results. I used the effectiveness rate of EBR/GRZ of 98%. Using equation (1), the annual probability of attaining SVR is 0.6247. The same principle approach was used to calculate transition probability from F0-F4 to SVR F0-F4 for all three strategies compared. The probabilities of SVR for LDV/SOF and pegIFN/RBV were calculated likewise.

3.4 Setting and perspective

The model-based economic evaluation follows the aim to consider the resource consumption in decisions related to healthcare. Therefore, it is important to consider all costs related to the healthcare issue. First, it is necessary to identify all the cost components that should be included into the analysis. Secondly, it is needed to quantify the use of every cost component. Afterwards, it is very important to accurately assign the identified and quantified resources. [7]

The analysis is made from the healthcare payer perspective - Norwegian regional healthcare authorities that are responsible for budgets of HCV treatment since 2016. The focus is made on the direct medical costs associated with treating chronic HCV and liver diseases,

liver transplantation, post-treatment monitoring and follow-up, costs of health outcomes, comparator treatment costs. I tried to collect the information on the costs from different sources to reflect the real situation of the Norwegian national insurance scheme.

3.5 Half-cycle correction

The transitions between health states in Markov models are modeled to occur in the beginning or at the end of the cycle, whereas in the reality the transition occur in the middle of the cycle. It can lead to the over- or underestimation of the health outcomes and costs accumulated by the model. To avoid this, the costs and the health outcomes were half-cycle corrected. [65]

3.6 Time horizon

The analysis of the thesis is based on the patient-level data collected in 3-year period. But it seems that 3-year time horizon to be inappropriate for the cost-effectiveness analysis that requires a long period of time to make the results obvious. Moreover, CHC remains a long-lasting disease that can occupy years and decades before it can be diagnosed and treatment to be initiated, so a short-term horizon can be misleading and can produce bias results without measuring life-time health consequences of the intervention. Therefore, 75-year lifetime horizon is chosen for the analysis to reflect correctly the impact of the intervention.

3.7 Discount rate

75-year lifetime horizon makes it necessary to compare the future and today`s value of intervention. For this purpose, it is necessary to apply a discounting rate that convert the value to cash-equivalent value on a specific reference date. The reference date normally chosen for an investment is the start date of the future costs and revenues of the project. The cash-equivalent value is in such case referred to as the net present value. Hence, discounting facilitates comparison between, and ranking of, measures with economic effects that occur at different dates.

The guidelines of the Norwegian Ministry of Finance as well as numerous CEA-based studies consider 3% an appropriate societal discount rate. Thus, 3%-discount rate was used for costs and utilities. [66]

3.8 Health outcomes

A broader measure of the benefits of treatment is utility that is used to refer to the preferences of individuals or society that they can have of any particular set of health outcomes. Utility analysis is viewed as a useful technique because it applies health-related quality of life (HRQoL) adjustments to a given set of treatment outcomes, providing a generic outcome measure for comparison of costs and outcomes in different treatment options programs. [8]

According to the recommendations of the Norwegian Medicines Agency (NoMA) the primary health outcome when conducting pharmacoeconomic analysis is quality-adjusted life-years (QALY). [67] QALY is a generic measure that is calculated by combining the length of life and HRQoL that is possible to use across and within treatment option. The advantage of the QALY as a measure of health outcome is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) and combine these into a single measure.

A particular health state has an assigned utility value - HRQoL – that reflects physical, psychological and social well-being. The main reason of using HRQoL is that it recognizes the influence of other factors than physical on QoL. HRQoL has a numerical expression between 0 and 1 where 0 represents death and 1 represents perfect health. In some situations, there are health states values less than zero, that is worse than death.

The health outcome of the analysis can also be expressed in life years gained (LYG). Usually cost-effectiveness analysis is based on the comparison of two or more alternatives that is stated on either in terms of cost per unit of effect (cost per life year gained) or in terms of effects per unit of cost (life years gained per unit of cost).

In the study I used the costs per QALY gained to present the results of CEA.

3.9 Cost-utility analysis

The base of this thesis is cost-utility analysis (CUA) which is the type of economic evaluation, usually applied to guide decision makers to allocate resources in a way that leads to the maximization of benefits received from the health intervention for a given budget constraint. CUA is often referred as a variant of CEA. The main aim of CUA is to quantify the health outcomes from intervention in QALY, generic measure of health gain. Thus, that gives an opportunity to compare the interventions from different areas of health care sector. CUA is a

useful tool for decision-makers with issue of allocating budget resources between health care interventions. [8]

The analysis is performed to compare the incremental costs per unit of effectiveness known as the incremental cost-effectiveness ratio (ICER) which estimates the additional cost per QALY associated with one intervention relative to other interventions. The results will give the LYGs and QALYs gained. The results obtained will be compared by calculating ICER and will be plotted on the cost-effectiveness plane. ICER is calculated by following formula:

$$ICER = \frac{Cost(DAA) - Cost(pegIFN)}{QALY\ (DAA) - QALY\ (pegIFN)} = \frac{\Delta Costs}{\Delta QALYs}, \quad (2)$$

The final verdict on cost-effectiveness of the strategy will be dependent on assessment of an appropriate threshold. If the cost-effectiveness of a new intervention is estimated below the threshold value, then it can be considered as cost-efficient. The net health benefits are calculated also basing on simulations and the threshold. A net health benefit (NHB) is the health accumulated among the population analyzed assuming that cost-effectiveness threshold represents the opportunity cost of the resources invested in the healthcare interventions. [8] The positive incremental NHB represents the accumulated overall health effects of the new intervention. In case of negative NHB the positive effects of the new intervention are outweighed by the costs. Any decision to accept or to reject the intervention which offers health benefits for additional costs still imply possible values for a threshold. Hence, implicit or explicit assessment of cost-effectiveness threshold should be conducted. [8]

According to the decisions of NoMA and the Norwegian Decision Forum (Beslutningsforum for nye metoder) the costs per QALY (ICER) should be estimated by the threshold values in the range 600 000 – 700 000 NOK per QALY. [68] The Norwegian Directorate of Health suggests this threshold per QALY for 2016. Without this condition any new intervention stays under consideration. Nevertheless, there is a wide discussion around ICER and its general applicability for all diseases. Many experts imply that the value of ICER should depend on the health effects and severity of disease: as much health is lost – as higher the ICER can be. The discussion was initiated by the working group of experts headed by professor Jon Magnussen. According to this report the WTP threshold should relate to the absolute shortfall caused by the severity of the disease, where the lowest WTP threshold 275 000 NOK relates to the loss of 0 – 3.9 healthy life years during the life time and the highest WTP threshold of 825 000 NOK corresponds >20 healthy life years lost during the life time. This approach has its' strengths and weaknesses that will be discussed further. But still the role

of ICER is debated and the threshold costs of 600 000 – 700 000 NOK per QALY is mostly considered as recommendation than a strict rule.

3.10 Sensitivity analysis

Sensitivity analysis is a tool to analyze the impact of uncertainty in CUA. The main aim of using sensitivity analysis is to assess and quantify the impact of uncertainty on the model outputs, e.g. ICERs as the results of the uncertainty in inputs, thus, to contribute to better decisions and to check if the model is working appropriately. It is also referred to a model validation. [69]

3.10.1 Deterministic sensitivity analysis

The deterministic and probabilistic types of analysis were conducted to see how the changes of some variables of interest influence the result. One-way sensitivity analysis is always performed on a variety of utility and cost parameters to see how sensitive the final result (ICER) to the small changes in the input data (parameters of interest) and if it crosses the threshold of interest.

One-way sensitivity analysis shows the changes in outputs by making changes in the value of a baseline parameters in a plausible range while other parameters stay constant. [70] That helps to identify the parameter of a high importance for the analysis without giving any quantitative indication of decision uncertainty, so there is still the risk of making a wrong decision. The model in this study is complementary, the number of the input parameters is too high to make the conduction of one-way sensitivity analysis of all parameters possible. Especially it relates to the transition probabilities.

3.10.2 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) is a recommended approach of NoMA and NICE when assessing cost-effectiveness of intervention. [67] PSA was undertaken according to the methods laid out by Briggs et al. [71] The main role of the PSA is to capture the parameter uncertainty by addressing the uncertainty in several parameters simultaneously and quantify the uncertainty surrounding the output of the model and, consequently, the decision uncertainty that the deterministic analysis is not capable to do. [69] To do this every uncertain parameter is

replaced with a distribution according to the confidence interval of the mean. Distribution types are used according to the specific characteristics of each parameter.

Beta distribution is used for rates, probabilities, QALYs, some of the resource-use measures. The main feature of beta distribution is that it was used a binominal probability parameter. It is constrained between 0 and 1, and the contingency between binominal data and binominal distribution makes it the most adequate choice in the context. Alpha is defined as the number of events observed, beta is the total number of observations minus alpha. [71] In most of the situations alpha was the number of the HCV infection events and beta was the total number of life years over which alpha was observed minus alpha.

Dirichlet distribution was used for multinomial probability parameters. To be more precise, all parts of multinomial probability are combined as a series of conditional beta distributions. [71]

Log-normal distributions are applied for the relative risks which are comprised of ratios that corresponds to confidence intervals and standard errors are calculated on the log scale. So, the log-normal distribution is the best choice. For a random draw from a normal distribution the natural logs of the point estimate and the standard error are used as alpha and beta respectively. The exponential yields a random draw based on the initial relative risk mean point estimate. [71]

Monte Carlo simulation was performed as it is usually used to estimate the distribution of the outcomes when it is impossible or impractical to determine the distribution theoretically. The model was simulated 1000 runs using the random draws for every parameter with its distribution. The results are the probabilistic output that give clearer scale of uncertainty surrounding point estimates and mean output. [71]

The outputs of PSA were recorded and used to estimate ICER, the incremental net monetary benefit (NMB) and expected value of perfect information (EVPI). The net monetary benefit (NMB) is calculated for every WTP threshold of interest (λ):

$$NMB=\lambda*E - C, \qquad (3)$$

where E denotes the effect of the treatment (QALY) and C is the costs associated with the treatment.

The cost-effective intervention has the NMB higher than the NMB of the comparator. Afterwards it is necessary to count the number of times the NMB of the intervention is higher and, thus, cost-effective. The proportion of times when the intervention has the highest NMB

identifies the probability of this intervention to be cost-effective. These probabilities can be calculated for the range of cost-effectiveness threshold values and presented as a graph or Cost-Effectiveness Acceptability Curve (CEAC). CEAC is plotted for every intervention and demonstrates which treatment alternative is cost-effective with higher probability. In contrast, the cost-effectiveness acceptability frontier (CEAF) shows the probability of cost-effectiveness of the treatment option expected to be cost-effective at every threshold value. CEAC and CEAF are used for uncertainty discussion of the cost-effective treatment option.

3.10.3 Expected Value of Perfect Information

All decisions about treatment are made in conditions of imperfect information, and there is a risk that the decision that is taken can lead to opportunity loss. In this case cost-effectiveness accessibility frontier (CEAF) shows the levels of the cost-effectiveness threshold at which the option is optimal, however, the scale of uncertainty and the consequences of not choosing the best option are ignored. To reduce the decision uncertainty expected value of perfect information (EVPI) analysis measures the magnitude of difference the true preferred and alternative decisions. [72]

EVPI analysis can be performed from the PSA results. It is used to assess the expected cost of uncertainty according to the threshold values. EVPI reflects the difference between the value of benefits when decision is made with perfect information and the value of benefits derived from a decision made with current information, or, EVPI is the expected value of maximum NMB (with perfect information) minus the maximum NMB (with current information) in each Monte Carlo iteration:

$$EVPI = E\theta\ Max j\ NB(j,\theta) - Max j\ E\theta NB(j,\theta), \quad (4)$$

where *j* represents the comparators, and θ represents the uncertainty surrounding the decision. EVPI represents the maximum potential value of reducing uncertainty at any threshold of interest that can be considered as a measure of the opportunity loss that comes from decision making due to uncertainty. [71]

3.11 Budget Impact Analysis

The burden of chronic HCV has had a large national economic impact, the anti-HCV drugs are expensive, and the healthcare resources are insufficient to meet the requirements of current demand for treatment. Therefore, every approach focused on efficient allocation of the

resources would benefit the overall population and should be studied. The lack of treatment will lead to increase of disease burden due to HCV pathologies and related worsening of the health state of the positive patients.

Budget Impact Analysis (BIA) is a required condition for reimbursement authorities as a reimbursement submission. The main aim of BIA is to evaluate the changes in expenditures after a new intervention is adopted. The results of BIA can be used in process of planning the resource allocation along with CEA. BIA and CEA complement each other and can be freestanding or parts of a comprehensive economic assessment. [73] Administrators of national health care budgets, private insurance companies, etc. – all actors of health care system are highly interested in results of BIA to set the priorities while allocating resources. Since CHC is one of the most crucial social issues in most of the countries in the world, still it can`t be solved as the treatment costs are very high and the elimination of the problem is unaffordable.

Therefore, the budgetary consequences of introducing DAAs in treatment of HCV as a part of the national reimbursement scheme were estimated to assess the potential affordability. Budget impact analysis reflects the perspective of the budget holders, using a short time horizon (observed 5 years), with the discounted treatment costs.

4 Input and material

Model inputs were derived from the literature, systematic reviews and Norwegian population-based registers. Due to the absence of the Norwegian clinical trials the data on the transition probabilities, effectiveness rates and health utilities were collected from numerous studies, assessed beforehand for its appropriateness for the Norwegian perspective. The baseline characteristics used in Markov model in this study were partly derived from the NICE report devoted to the new anti-HCV regimens, including EBR/GRZ and LDV/SOF, meta-analysis and studies related to chronic HCV, its progression and treatment.

4.1 Transition probabilities

The transition probabilities were transformed basing on the age-specific all-cause death. The base case transition probabilities were adjusted to the probability of all-cause death and to sum it up to 1, and that was the main issue. For this reason, I multiplied age group-specific death probability on every transition probability and subtracted this proportional part from every transition probability and sum up to 1. The table with base case transition probabilities of is presented in Appendix 2.

For the probabilistic analysis mostly Dirichlet distribution was used in the model as there were more than two transition probabilities for each state (beta - for two states). Since there was a lack of the data on all the transition probabilities and absence of alphas and betas, the only solution was to apply the uniform random estimates with standard deviation of 10% of the mean base case value of every health state in the model, excepting just a few having alpha and beta (LT).

4.2 Health outcomes. Measurement and valuation

The measure of the health utility applied in the model was QALY that seeks to reflect the impact on length of life and HRQoL in a single measure. [39] QALY was chosen for this analysis as its nature corresponds the policy of prioritization of the Norwegian health care authorities [83]

EQ-5D was a base for the utility weights for this analysis as it is one of the most commonly used instruments. EQ-5D questionnaire is a generic preference-based health measure that has a structured health state descriptive system (questionnaire) with five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The health state preference-based values, or utilities of health states that have been measured by using the time-trade-off (TTO), visual analog scale (VAS), or standard gamble (SG), are converted by a scoring formula (or tariff) into a measure. The source of the values is the general public. [84] In my analysis I used the weighted average of the QALY values from the NICE Committee paper. In this paper EQ-5D was the main tool for adult population to estimate QALY influence of different technologies and for generating health state utility values. [85]

The utility weights are calculated by multiplying HRQoL of a health state by the time spent in the health state. The baseline utility weights of the health states are presented in the Table 2.

Table 2. Utility weights of health states associated with chronic HCV

Health states	**Mean**	**SE**	**Reference**
F0	0.77	0.02	[85]
F1	0.77	0.02	
F2	0.66	0.03	
F3	0.66	0.03	
F4	0.55	005	
SVR, F0 - SVR, F1	0.82	0.04	
SVR, F2 - SVR, F3	0.71	0.05	
SVR, F4	0.6	0.06	
DC	0.45	0.045	[86]
HCC	0.45	0.045	
LT	0.45	0.045	
PLT	0.67	0.067	

F0 – No fibrosis, F1 – mild fibrosis, F2 – moderate fibrosis, F3 – advanced fibrosis, F4 – Compensated cirrhosis, SVR – sustained virologic response, DC – decompensated cirrhosis, HCC – liver cancer, LT – liver transplantation, Post-LT – subsequent years after LT, SVR – sustained virologic response.

4.3 Age-specific parameters

Age is an important factor for the treatment of HCV-infected patient as it can influence on continuity of the therapy, possible adverse events, effectiveness of the drug, appearance of other diseases, comorbidities and even death caused by age. For this reason, I included age-specific utilities and background (all cause) death probability into this analysis as the health state depends on physical and psychological wealth - as older the patients are as more health problems they have, as lower the HRQoL values of patients. Age impacts perception of the health state through other health problems and the EQ-5D scores while evaluating the health-related outcomes of the treatment. That was reflected in the analysis by multiplying the age-specific utilities by the utilities summarized for one cycle.

Age-specific utilities were derived from the Medical Expenditure Panel Survey (MEPS) [87] that is an American representative survey of the US civilian noninstitutionalized population with information collected about demographic characteristics, health conditions and status. The age-specific HRQoL weights associated with any health state from the model is presented in the Table 3.

For the probabilistic analysis I applied beta distribution that is appropriate for health utility parameters using standard error derived from the survey mentioned.

Table 3. Age-specific baseline utilities

Age group	**Mean**	**Standard error**	**Distribution**	**Source**
≤29	0.92	0.0019	Beta	[87]
30-39	0.901	0.0021	Beta	
40-49	0.871	0.0024	Beta	
50-59	0.842	0.0028	Beta	
60-69	0.823	0.0034	Beta	
70-79	0.790	0.0036	Beta	
≥80	0.736	0.0062	Beta	

As it was mentioned earlier Markov model includes age-specific background (all-cause) death. The all-cause death rates were based on the population size and mortality rates per 100 000 citizens of each age group (20-29, …,80-89) obtained from Statistics Norway. [88] Age-specific event rates were converted into transition probabilities by using equation (1) to be applied in the Markov model according to methods described by Briggs et al. [71] The results are shown in the Table 4.

For the probabilistic analysis I used the same approach as in case with transition probabilities – uniform random values with standard deviation of 10% for every mean value of the all-cause death for each health state in age group.

Table 4. Age-specific all-cause death rates and probabilities

Age group	Population size	Death rate per 100,000	No deaths	Death rate	Probability (Mean)	Range Lower limit (0.9)	Range Upper limit (1.1)
20-29	711 240	0.00161	1 145	0.00161	0.00161	0.00145	0.00177
30-39	700 025	0.00208	1 456	0.00208	0.00208	0.00187	0.00229
40-49	741 730	0.00435	3 227	0.00435	0.00434	0.00391	0.00477
50-59	670 553	0.01226	8 221	0.01226	0.01219	0.01097	0.01340
60-69	570 671	0.03344	19 083	0.03344	0.03289	0.02960	0.03618
70-79	380 388	0.09470	36 023	0.09470	0.09035	0.08132	0.09939
80-89	176 371	0.33455	59 005	0.33455	0.28434	0.25591	0.31277

Source: Statistikkbanker på folkehelseinstituttet (Statistics Banks from the National Institute of Health) [Internet]. [cited 2017 September 28]. Available from: http://statistikkbank.fhi.no/webview

4.4 The costs associated with treatment of the chronic HCV

The type of costs included in the model aimed to reflect the direct costs that relate to the clinical management of patients with chronic HCV: cost of medication, treatment (consultations at the general practitioner, hospitalization), monitoring and follow-up, management of complications related to adverse events. Monitoring costs refer to the costs that incur while patients are being treated with the drug prescribed: LDV/SOF, EBR/GZR or pegIFN.

Data on the costs connected with treatment and care of chronic HCV are limited. To find any information on the quantity and price of the resources I used all available studies and guidelines relating the treatment of every health state of chronic HCV applied in the Norwegian perspective. The opinions of clinical experts were also considered and were sometimes the main source of information. All costs are in Norwegian kroner (NOK). Summarized health costs are presented in Appendices 2, 3, 4, 5.

The costs of the drugs for treatment were estimated using the pharmacy price, provided by the NoMA medicine database. The analysis includes also the average annual quantity of doses used per patient as was acquired by the Norwegian Prescription Database. According to

the official decision of NoMA the costs associated with HCV drugs should be based on the principles developed by Tollefsen and colleagues. [47] For the purpose of consistency of the Norwegian economic evaluations the same approaches were applied in this analysis – all costs were based on the Norwegian average in- and outpatient treatment [89] and official fares for the primary care treatment.

In Norway, a diagnostic-related groups (DRG)-system is used to get an overview of the type of activity and costs at the hospitals when treating the somatic diseases. DRG provides both medical and financial information. [3] There is also in use the term Major Diagnosis Category (MDC), which the principal diagnosis of the patient indicates. This includes, first, DRGs for highly specialized and expensive care. All diseases of the liver, bile ducts and pancreas relate to the code MDC-7.

In my analysis I used the information found from DRG-codes that relate to the liver diseases (fibrosis, cirrhosis, liver cancer, liver transplantation), including the consultations, hospitalization, diagnostics, treatment follow-up and management.

In Appendix 2 all activities relating the treatment of the liver disease are presented and considered in calculation of the treatment costs.

Appendix 3 contains the price per unit cost with DRG-code and DRG-weight that correspond the price. Unit price per DRG point in 2014 is set at 40 772 NOK. [89] The DRG-weights reflect the relative cost of providing care in each DRG in the hospital per average patient, forming the basis for the activity-based funding. The higher the weight, the more DRG points and the higher income for in-patient days in the DRG.

Table 4 (see Appendicles) contains the information on the laboratory tests (excluding assumed 0,5-hour fee for service of the nurse for blood sampling and administration).

The annual costs for health care services are different for new and old standard therapies as the length of the old standard treatment is 48 weeks instead of 12 weeks with DAAs, moreover the side effects of the pegIFN-based treatment can be very severe and require additional clinical help. To follow the patient and eliminate the consequences of side effects in the right time the patient, passing through the pegIFN-therapy, visit hospital for consultation with GP and for blood sampling every 2 weeks during the treatment and 2 times after the therapy is ended (after 1 and 6 months). For this reason, the costs of IFN-based treatment at stage of

[3] NordDRG is used by the Nordic countries, including Norway since 1999. This system is adopted according to the national adjustments.

fibrosis include more consultations with GP (10 per year), additional blood tests (10 per year, including 0,5-hour fee for nurses for blood sampling and administration).

The DAA-based therapy includes the follow-up and consultations at GP at week 4, 8, 12 the medicament treatment and 1-2 times during 24 weeks after the therapy is ended.

The fees for services of different healthcare personnel is taken from the Tariffs for GPs and heath care personnel [in Norwegian: Normaltariff for fastleger og legevakt] 2013-2014 submitted by the NoMA. Table 5 includes the total costs associated with each stage of liver disease caused by chronic HCV infection. These figures were used in the model.

Table 5. Annual costs per stage of liver disease caused by the chronic HCV infection, by treatment strategy (NOK, per patient)

Health states	With DAAs	With pegIFN/RBV
F0-F1	13 631	28 682
F2-F3	16 179	28 682
F4	25 542	53 961
SVRF4	5 789	5 526
DC	258 767	257 582
HCC	353 031	353 031
LT	1 705 000	1 705 000
Post-LT	140 290	140 290

F0 – No fibrosis, F1 – mild fibrosis, F2 – moderate fibrosis, F3 – advanced fibrosis, F4 – Compensated cirrhosis, SVR – sustained virologic response, DC – decompensated cirrhosis, HCC – liver cancer, LT – liver transplantation, Post-LT – subsequent years after LT, DAA – direct acting antiviral, pegIFN/RBV – Pegylated Interferon/Ribavirin.

The costs include follow-up, hospitalization, consultations, lab-tests, excluding cost of medication. For LT, the costs include In-patient treatment of transplanted.

Drug costs were taken from the published resources in Norway. I used the sale price from the Norwegian Pharmaceutical Product Compendium (Felleskatalogen) per one package. Table 5 (Appendices) contains the costs of drugs used in the treatment of treatment-naïve HCV GT1 infected patients.

Gamma distributions was used for costs. Costs are typically represented by the Poisson distributon that is characterized by a bound from 0 to infinity that makes gamma distribution appropriate. Use of gamma also allows for rightward skewedness that can reflect expensive outliers that are sometimes observed in cost data. [71] The assumption applied for the parameters of the gamma distribution was that the standard deviation of each cost was 10% of

the calculated mean, thus the upper and lower limit of the 95% confidence intervals are accordingly 20% lower/higher than the mean values. If expected value and variance are known, but alphas and betas are unknown, it is possible to use the following equations (6) and (7):

$$\alpha = \frac{expected\ value^2}{standard\ deviation^2} \quad (6)$$

$$\beta = \frac{standard\ deviation^2}{expectd\ value} \quad (7)$$

5 Results

5.1 Cost-effectiveness of treatment with DAAs vs. pegIFN/RBV

The deterministic analysis results for different strategies applied to the base-case patients cohort are shown in the Table 6, showing the ICER versus old standard therapy. The expected costs per patient cohort was established for three treatment strategies separately. Incremental cost-utility ratio (ICUR) was calculated for Zepatier and Harvoni against old standard pegIFN-based therapy. The results represent mean values of costs per patient. The expected life-time costs per patient for Zepatier and Harvoni were established on the level 1 747 748 NOK and 1 882 326 NOK respectively, whereas in pegIFN-group the expected costs were 961 541 NOK. The expected QALYs gained are the following: incremental 1.098 QALYs with Zepatier and 1.094 QALYs with Harvoni per patient for 75-years' time horizon. ICUR calculated was 716 158 NOK per QALY gained with Zepatier and 841 727 NOK - with Harvoni. Both DAAs are almost same clinically effective for the almost the same costs, but Zepatier (EBR/GRZ) is still considered economically dominating giving the same number of QALYs gained with lower incremental costs.

Table 6. Results of deterministic analysis of HCV treatment. Life-time outcomes of the old standard treatment and DAAs (per patient)

Therapeutic option	Total costs	QALYs gain	Costs per additional QALY	Life-time costs for drugs, NOK	Life-time costs for medical services, NOK
pegIFN/RBV	961 541	15.507	-	640 523	321 050
EBR/GRZ	1 747 748	16.605	716 158	1 546 532	201 216
LDV/SOF	1 882 326	16.601	841 727	1 597 907	284 419

EBR/GRZ, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; ICUR, incremental cost-utility ratio; LY, life years; pegIFN/RBV, peg-interferon; RBV, ribavirine; QALY, quality-adjusted life years.

The cost of DAA-based therapy per 1 patient is higher over a lifetime in comparison with old standard treatment. The costs for drugs are 640 523 NOK, 1 546 532 NOK and 1 597 907 NOK for pegIFN/RBV, EBR/GRZ and LDV/SOF therapies respectively. Whereas,

the costs for health care services over a lifetime for 1 patient are 321 050 NOK, 201 216 NOK and 284 419 NOK for therapies with pegIFN/RBV, EBR/GRZ and LDV/SOF respectively. The QALYs gained by therapy with EBR/GRZ and LDV/SOF are 16.605 and 16.601 respectively while the therapy with pegIFN/RBV achieved clearly less (15.507). It means that the DAA-based therapy gives more than 1 additional QALY in comparison with old standard therapy. According to the results EBR/GRZ can be suggested as an optimal treatment alternative than LDV/SOF because of additional 0,005 QALYs achieved for lower costs.

Basing on the results of the deterministic analysis, I can conclude that the high costs of treatment strategies with DAAs seem reasonable for the health effects they provide and number of avoided cases of advanced liver disease that are costly for health care budget.

Probabilistic analysis was conducted for LYs and QALYs separately for both drugs of the analysis - EBR/GRZ and LDV/SOF. The results are derived from 1000 iterations in the PSA and presented in the Table 7.

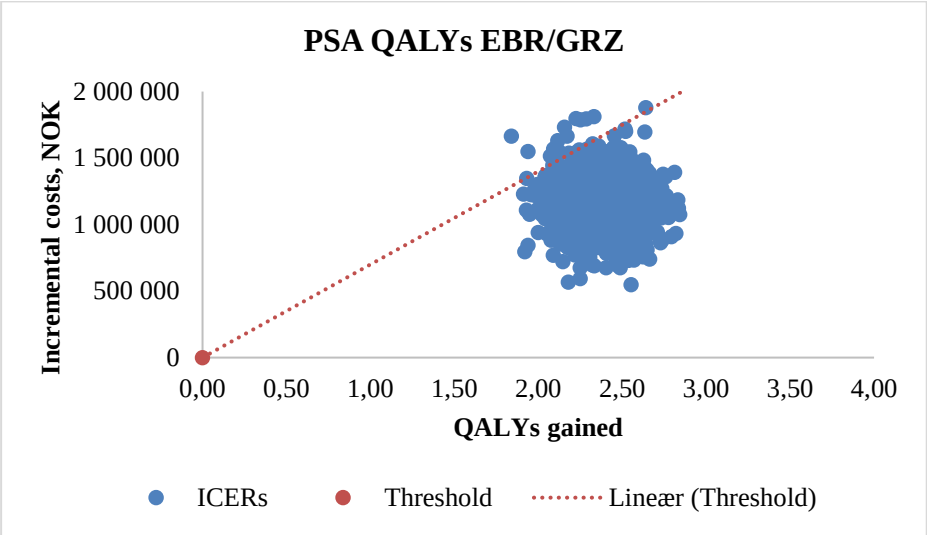
Table 7. Results of probabilistic sensitivity analysis (per patient)

	Intervention	Mean costs (95 % CI)	Mean QALYs (95 % CI)
1	**Old standard practice**	1 031 749 (841 661 – 1 248 352)	11.57 (9.67 – 13.09)
2	**EBR/GRZ**	2 176 740 (1 606 488 – 2 927 274)	13.94 (11.88 – 15.73)
2.1	**Mean Difference (2-1)**	1 144 992 (547 927 – 1 878 355)	2.37 (1.84 – 2.84)
3	**LDV/SOF**	2 313 831 (1 715 591 – 2 940 025)	13.94 (11.66 – 16.22)
3.1	**Mean Difference (3-1)**	1 282 082 (873 930 – 1 691 673)	2.37 (1.93 – 3.13)

The cost-effectiveness plane in the Figure 3 demonstrates the results of the PSA for QALYs for EBR/GRZ compared with pegIFN/RBV. On the figure most of the points corresponding ICERs are concentrated in North-East quadrant of the coordinate system. That means that this treatment strategy has higher costs and provides additional life years during the life time horizon. For this analysis the highest level of the willingness to pay (WTP) threshold

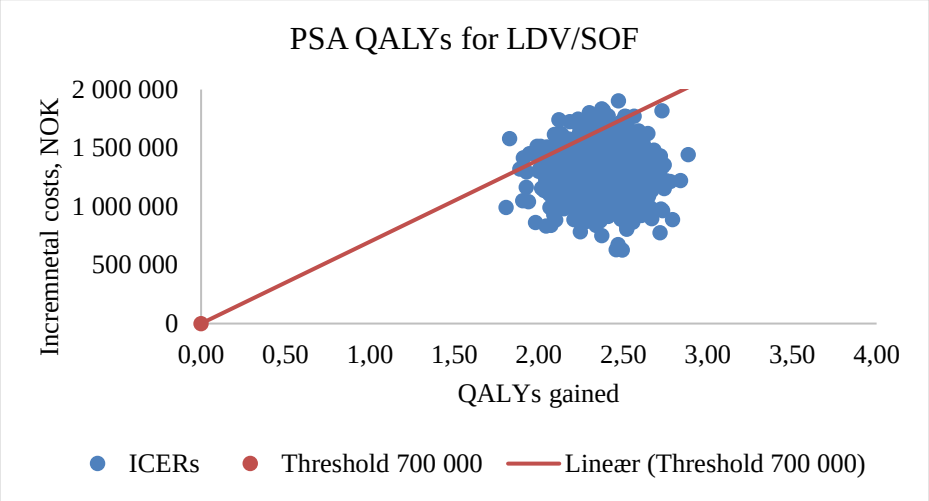
was taken at the level of 700 000 NOK. WTP threshold is used as a limit price that the payer is ready to pay for additional QALY. As we can see on the graph, all points are under the threshold line that practically can mean the cost-effectiveness of the treatment with EBR/GRZ. As more points are laying under the threshold line, as higher the probability of EBR/GRZ being cost-effective at this threshold.

Figure 2. Cost-effectiveness plane for QALYs



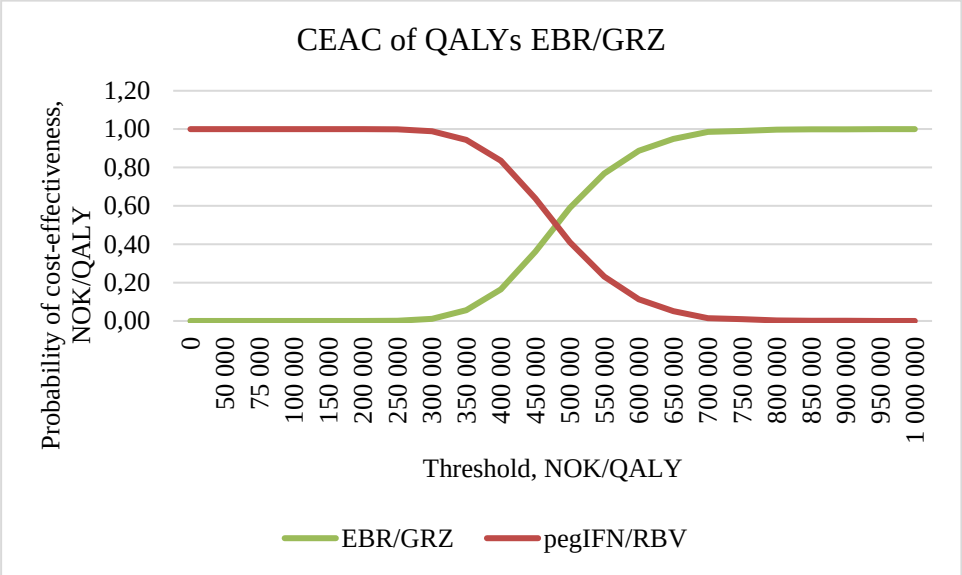
The cost-effectiveness plane of PSA for QALYs gained of LDV/SOF is presented in the Figure 4. The WTP threshold was the same 700 000 NOK and the ICUR points were concentrated in North-East side of the coordinate system proving the cost-effectiveness of the therapy vs. the old standard therapy.

Figure 3. Cost-effectiveness plane for QALYs



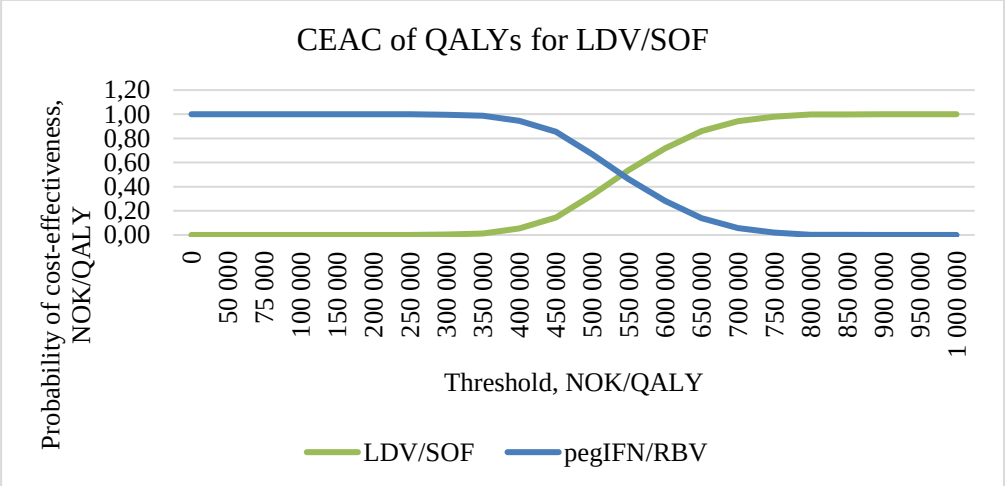
The CEACs of QALYs for EBR/GRZ vs. pegIFN/RBV and LDV/SOF vs. pegIFN/RBV are presented in the Figures 4 and 5 respectively. It is possible to see that both drugs are cost-effective at WTP-threshold of 700 000 NOK. The CEAC shows that at threshold 700 000 NOK EBR/GRZ is cost-effective with 99% probability and with probability of 59% at threshold of 500 000 NOK for additional QALY (Figure 4).

Figure 4. CEAC of QALYs



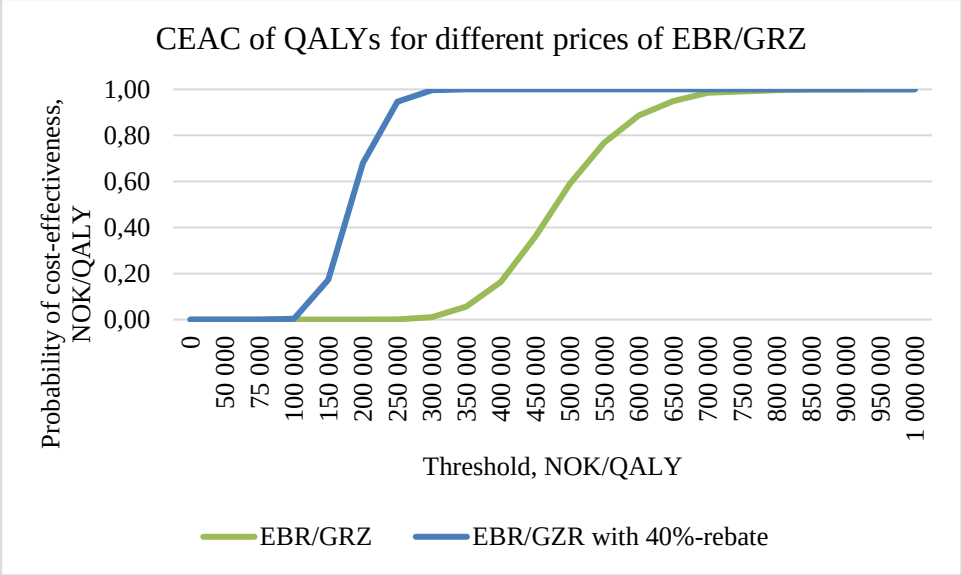
According to the CEAC in the figure 5 Harvoni (LDV/SOF) is cost-effective with probability 46% at the WTP-threshold 550 000 NOK and with probability 94% at the WTP-threshold 700 000 NOK. As a result, the treatment option with EBR/GRZ can be suggested as optimal treatment option.

Figure 5. CEAC for QALY



In the Figure 6 the CEACs of QALYs for different price levels of Zepatier are presented: the first one corresponds the standard wholesale price and the second – the assumed price with 40%-rebate. It is important to know the probability of being cost-effective of Zepatier with new price that, unfortunately, is not available in published sources. As we can see from the Figure 6, this probability is very high - around 95% with ICER equal 250,000 NOK. We can suggest that DAA-therapy seems very favourable for patients for its effectiveness and tolerability and for the payer side – because of the lower prices that can create the possibility to treat patients from the early stages and avoid advanced liver diseases saving money for the medical services.

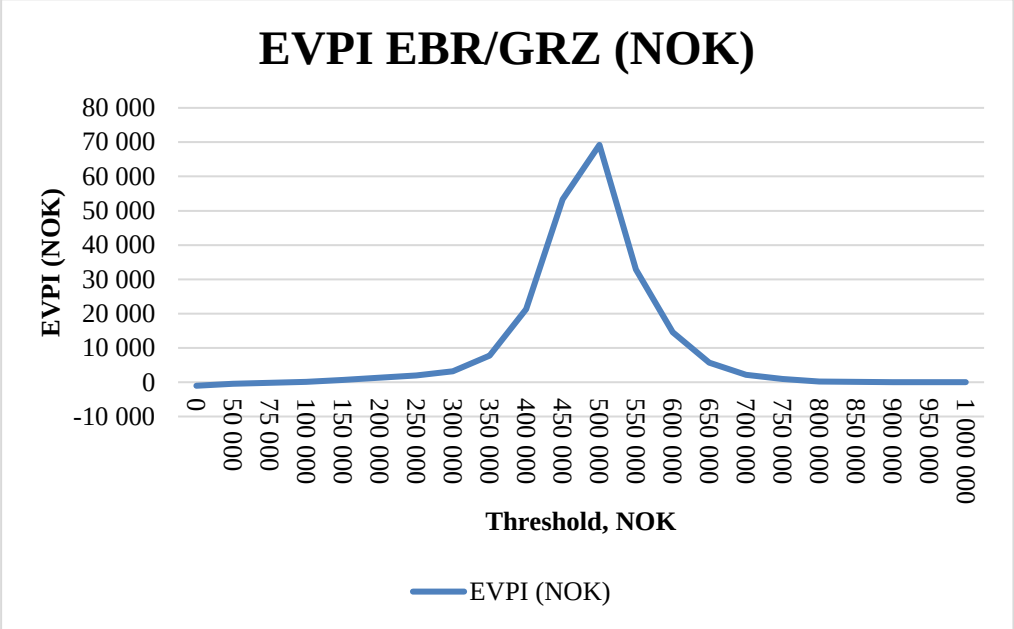
Figure 6. CEAC of QALYs



The results of CEA show that EBR/GRZ is cost-effective with WTP threshold of 700 000 NOK with higher probability (99%) compared with LDV/SOF (94%) for treatment-naïve genotype 1 HCV mono-infected patients. CEAC suggests that at WTP-threshold 500 000 NOK the probability of cost-effectiveness of EBR/GRZ and LDV/SOF are 59% and 33% respectively that suggests LDV/SOF as non-cost-effective if the WTP-threshold is lower than 700 000 NOK assumed. It may be considered that EBR/GRZ is still an optimal treatment option for different levels of WTP-threshold.

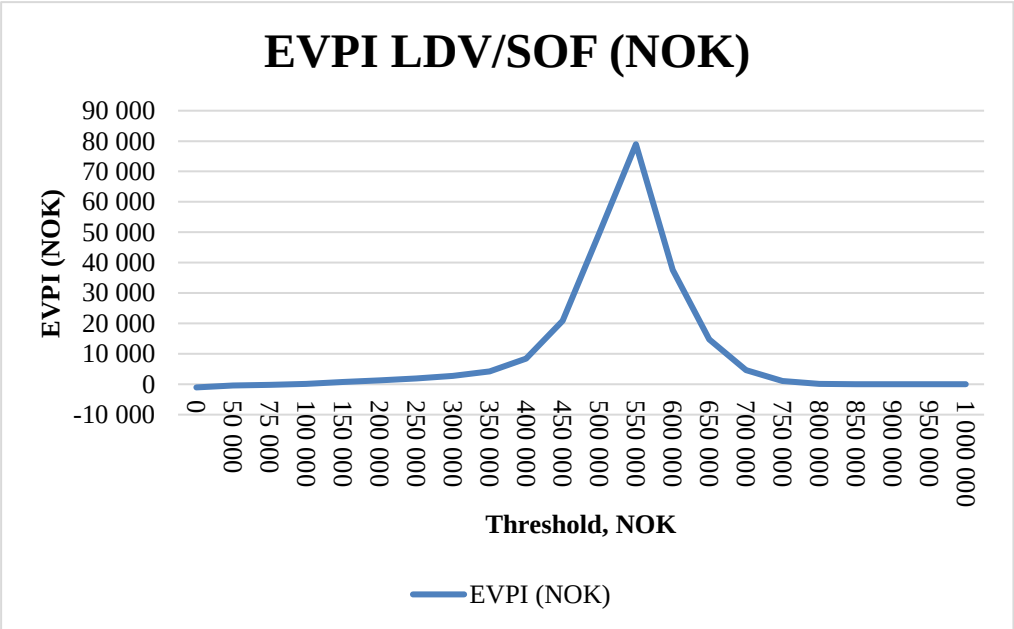
The expected value of perfect information is conducted for QALYs of EBR/GRZ and LDV/SOF. The EVPI for EBR/GRZ is the highest when the WTP is 500 000 NOK (Figure 8), as well as the highest EVPI for LDV/SOF is at the WTP 550 000 NOK (Figure 9) that confirms the results of CEACs that is shown in the Figures 5 and 6 respectively.

Figure 7. Expected value of perfect information



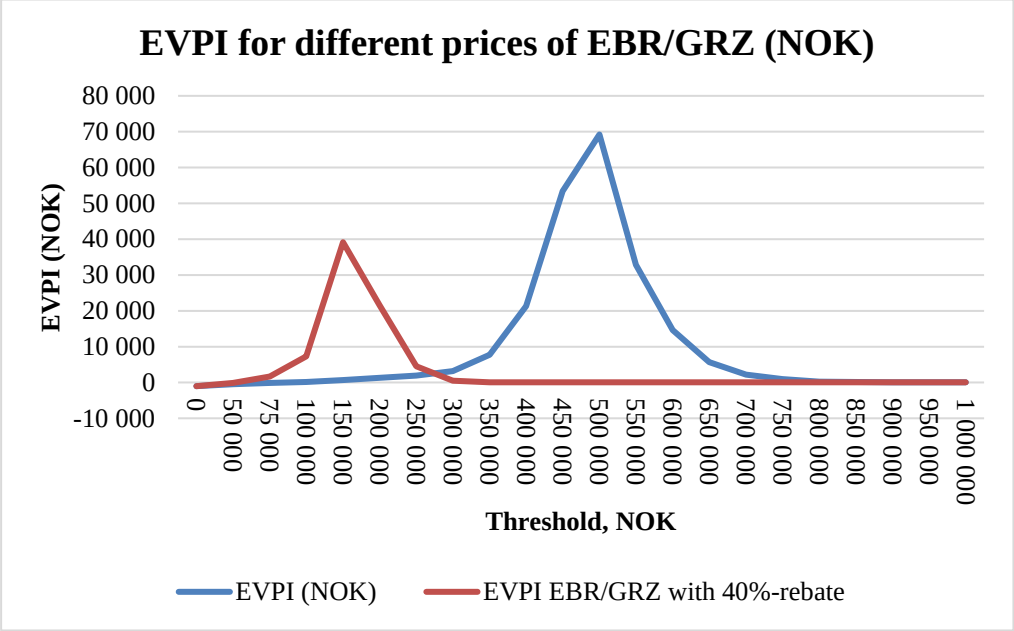
If two interventions have the same probability of being cost-effective, it creates additional uncertainty about what intervention is optimal. The EVPIs of both drugs correspond the points of CEACs. At WTP of 500 000 NOK, the EVPI is 69 213 NOK for EBR/GRZ and 78 962 NOK for LDV/SOF suggesting that EBR/GRZ is an optimal treatment option.

Figure 8. Expected value of perfect information



To know the EVPI for the price rebated, the CEAC and EVPI evaluation for the assumed price can be conducted. But we can assume also that the rebated price for drugs can demonstrate more favourable results of cost-effectiveness, but still it is included in the analysis to make the conclusions more visible. The EVPI for both price regimes are presented in the Figure 10. At WTP 150 000 NOK EVPI is 39 142 NOK that was expected.

Figure 9. Expected value of perfect information



5.2 Budget Impact Analysis

The issues of the staging of HCV when the therapy should be initiated and the high prices of DAAs are the most debated by the health care authorities responsible for planning and financing. For this reason the BIA incudes several scenarios of DAA-based treatment. The analysis will be devoted only to EBR/GRZ as the effects of EBR/GRZ and LDV/SOF are almost the same, so the conclusions of BIA will relate to both regimens. The scenarios are the following: 1) Therapy with pegIFN/RBV for 48 weeks. 2) Therapy with EBR/GRZ for 48 weeks. As the price of EBR/GRZ was rebated, but publicly not available, the sensitivity analysis was conducted for a 40%-rebated price for 12-week therapy of EBR/GRZ.

The methods were used according to International Society for Pharmacoeconomics and Outcomes (ISPOR) task force report by Sullivan et al. [91]

The analysis as well as the study is based on the principles of the Norwegian healthcare sector that is characterized by the public financing from the Norwegian National Health Insurance Scheme – from payer`s perspective.

According to the guidelines of Norwegian Ministry of Finance 3% is an appropriate societal discount rate for the project above 40 years. [66] 3% discount rate is applied in the study, though it is generally not required.

BIA presupposes estimates the financial consequences of adopting a new intervention. The size of the population is explicitly considered in BIA to evaluate the total budget required for fund intervention. The overall number of HCV infected patients in Norway is assumed to be 16 500 (11 000 – 17 000 by the NIPH). By MSIS, 44% are presented by the GT1, so the number of patients used in BIA is 7 260. The distribution of the patients for the first scenario is 4 719 at METAVIR F2 stage, 1 089 at stage F3 and 1 452 patients – at stage F4 corresponding the proportions 65%, 15% and 20% respectively.

The cost of the therapy, of the management of adverse events and health state were the same used in the model: taken from the published resources, calculated using activity-based approach, through interviews with clinical experts.

The results of the analysis are reported in the Table 8. The use of EBR/GRZ will lead to the increase of the costs for the Norwegian Health System (NHS) in 5 years considered in the analysis. To be more precise, the costs increase due to the costs of treatment, while the costs related to the management of the health state (HS) and follow-up of the adverse events (AE) are almost twice lower. This trend is followed during all 5 years. The total impact on the budget of the NHS mostly decrease during all 5 years (-70%, -25%, -43%, +8%, -24%).

Table 8. Impact on the NHS of the use of EBR/GRZ for the treatment of HCV genotype 1 infected patients (treatment is initiated at fibrosis stages F2-F4 for base case price), million NOK

		Costs (mln NOK)					
Scenario	**Cost category**	**Year 2014**	**Year 2015**	**Year 2016**	**Year 2017**	**Year 2018**	**Year 2019**
pegIFN/RBV 48 weeks	Treatment	1032	463	286	177	135	106
	HS and AE	245	140	143	158	182	203
	Total	1277	603	429	335	317	309
with EBR/GRZ 12 weeks	Treatment	3746	1302	921	564	563	465
	HS and AE	131	78	90	98	107	110
	Total	3877	1380	1011	662	670	575
Budget impact	Treatment	2714	839	635	387	428	359
	HS and AE	-114	-62	-53	-60	-75	-93
	Total	2600	777	582	327	353	266

Due to the absence of the published rebated price of EBR/GRZ, it was assumed that the rebate was 40%, and the results of BIA are presented in Table 9. The total impact with rebated price of EBR/GRZ compared to the base case price is 57%, 67%, 56%, 70%, 63% lower in the subsequent years considered in the analysis.

Table 9. Impact on the NHS of the use of EBR/GRZ for the treatment of HCV genotype 1 infected patients (treatment is initiated at fibrosis stages F2-F4 for 40%-rebated price), million NOK

		Costs (mln NOK)					
Scenario	**Cost category**	**Year 2014**	**Year 2015**	**Year 2016**	**Year 2017**	**Year 2018**	**Year 2019**
with pegIFN/RBV 48 weeks	Treatment	1032	463	286	177	135	106
	HS and AE	245	140	143	158	182	203
	Total	1277	603	429	335	317	309
with EBR/GRZ 12 weeks	Treatment	2248	781	553	338	338	279
	HS and AE	131	78	90	98	107	110
	Total	2379	859	643	436	445	389
Budget impact	Treatment	1216	318	267	161	203	173
	HS and AE	-114	-62	-53	-60	-75	-93
	Total	1102	256	214	101	128	80

Impact of treatment initiation by fibrosis stage (F0 vs. F2-F4)

The discussion about the timing of treating HCV is getting wider. [94] From one side, for the reason that part of the patients (approximately 30%) are getting rid of the virus on the early stages of fibrosis without treatment, it was considered more reasonable to initiate the therapy at the moderate or advanced stages of fibrosis as it is associated with lower costs. To get more information on the economic impact of the postponed treatment, BIA included the part where two approaches were compared: treatment with EBR/GRZ of HCV genotype 1 infected patients with moderate and advanced fibrosis and the same therapy but initiated at stage of absence of fibrosis (F0). The results are presented in Table 10. The treatment costs of the early treatment are the same like in postponed treatment in the 1st year, 9% higher in the second year and have the decreasing trend in the subsequent years (-37%, -40%, -55%). The medical costs related to the management of AEs and follow-up are much lower if HCV is treated early: -24%, -54%, etc. It can relate to lower incidence of the advanced liver diseases if HCV is treated at early stages. The total impact on the NHS of the postponed HCV treatment is significant (32, 2, 414, 317 and 412 million NOK) during the whole period of analysis.

Table 10. Impact on the Norwegian Health System of the use of EBR/GRZ for the treatment of HCV genotype 1 infected patients if therapy initiated at stages METAVIR F2-F4

		Costs (mln NOK)					
Scenario	**Cost category**	**Year 2014**	**Year 2015**	**Year 2016**	**Year 2017**	**Year 2018**	**Year 2019**
with EBR/GRZ (at stage F0)	Treatment	3746	1342	581	335	251	218
	HS and AE	99	36	16	9	7	6
	Total	3845	1378	597	344	258	224
with EBR/GRZ (at stage F2-F4)	Treatment	3746	1302	921	564	563	465
	HS and AE	131	78	90	98	107	110
	Total	3877	1380	1011	662	670	575
Budget impact	Treatment	0	-41	340	228	312	246
	HS and AE	32	42	74	89	100	104
	Total	32	2	414	317	412	350

EBR/GRZ – Elbasvir/Grazoprevir; HS – Health state; AE – adverse events

The limitation of the analysis can be the 5-year period analysed as HCV is a long-lasting disease and the direct medical costs increase in the long period (due to decompensated cirrhosis, liver cancer and liver transplantation), therefore the results of current BIA could be overestimated without consideration of the benefits. But basing on the results of 5-year analysis, there is a trend of the costs reduction with EBR/GRZ compared with pegIFN/RBV, which may lead to the reduction of the costs in a long term. Additionally, the economic and health benefits of the early treatment with EBR/GRZ were also very favourable.

5.3 One-way sensitivity analysis

Sensitivity analysis shows the influence of different variables on ICUR. Nonetheless, the model in this study is very complex (complementary) that makes it difficult to evaluate the influence of every variable. For this reason, the analysis included only the sensitivity analysis of the price of the interventions.

One-way sensitivity analysis for price of DAAs–to was conducted to evaluate the potential future results of the price rebated for the hospitals achieved during the tender negotiations between the Norwegian healthcare authorities and the pharmaceutical companies. The final prices are never publicly available, so the results of a one-way sensitivity analysis can help to understand the financial impact of new prices on the economic effect of the treatment analysed. The results are shown in the Figures 13 and 14. Moreover, numerous studies show small influence of most variables, excluding the most decisive like drug costs, age and discount rate. [5, 90, 92]

Figure 10. Results of one-way sensitivity analysis for QALYs

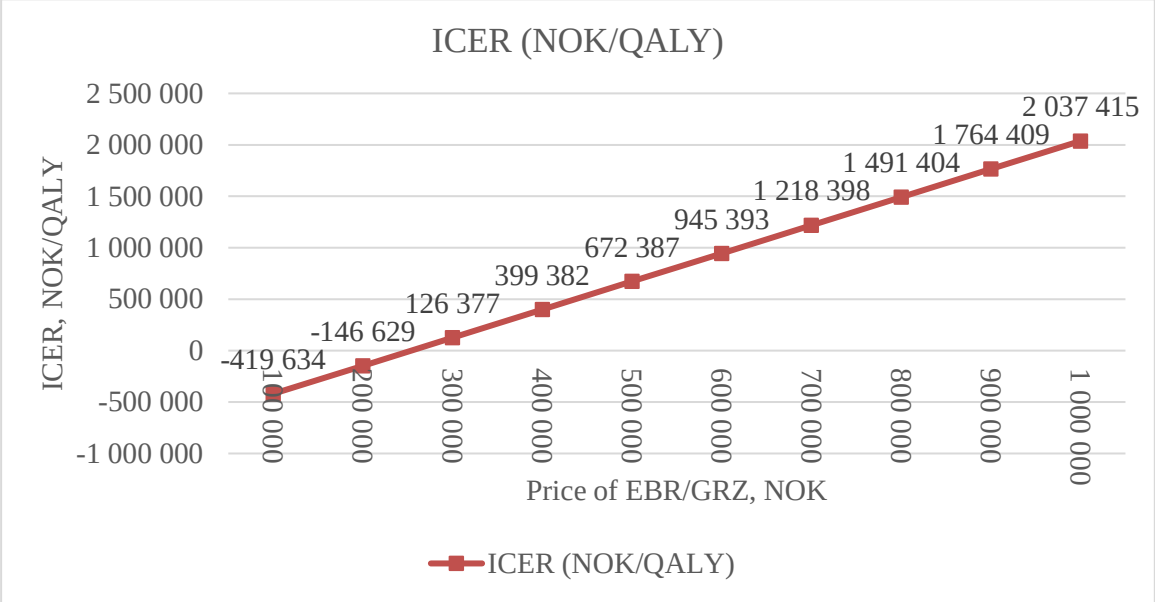
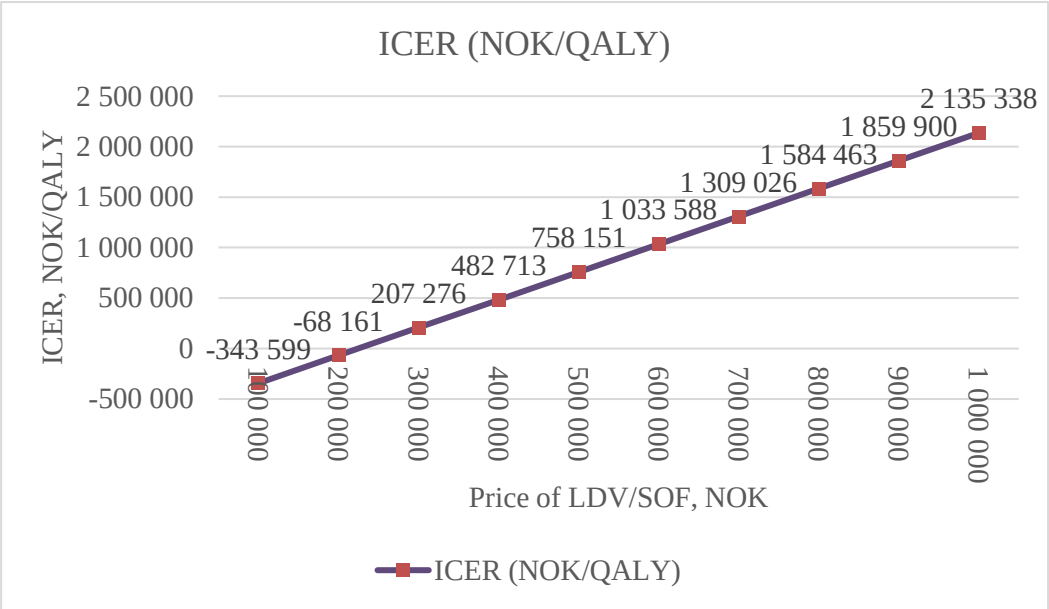


Figure 11. Results of one-way sensitivity analysis for QALYs



6 Discussion and limitations

This thesis is one of the first studies devoted to analysis of cost-effectiveness of EBR/GRZ in Norway. Though transition probabilities and utility weights were derived from non-Norwegian studies, the most input parameters and model characteristics reflect the Norwegian perspective. The analysis was based on the real practice, opinions of the clinical experts, actual patient data and the current national guidelines in modelling the long-term health and economic outcomes of different treatment strategies. Nevertheless, the thesis has the number of limitations connected with the uncertainty of parameters, structure of the model and assumptions.

In this study the WTP of 700 000 NOK was used for CEA, but there is a wide discussion among healthcare economists on usage of threshold as an effectiveness limit. For instance, the WTP threshold at the level of 600 000 – 700 000 NOK per QALY gained seems to be a desired recommendation rather than a strict national guideline for reason that, firstly, this threshold can be low in case of life threatening diseases [68], and secondly, it can seem misleading to hold strictly threshold without indicating borderline ICERs when intervention is considered cost-effective in the Norwegian healthcare system.

As it was mentioned above the prioritization principle proposed by Magnussen et al. can be a good alternative approach in identifying an appropriate level of WTP-threshold for a particular disease. In that case, the results of this study prove the cost-effectiveness of EBR/GRZ and LDV/SOF with WTP-threshold of 700 000 NOK per QALY gained as appropriate for treatment of CHC. Especially since chronic HCV is a dangerous disease as hardly diagnosed at the early stages, but associated with serious consequences for health if not treated and transmission to healthy people increasing the rates of mortality and morbidity. Nevertheless, this approach is widely debated. An appropriate health-loss criterion (or criteria) of every health condition still must be identified to avoid the omission of modifying factors (like uncertainty, dignity and budget impact) that can lead to acceptance of an intervention with a cost higher (or lower) than is commensurate with the measure's degree of severity. The working group is admitting that the approach should be adopted for the Norwegian perspective with consideration of the resource use for the intervention of interest. It seems to be very challenging as even the clinical experts cannot give the detailed information on all resources used for one QALY gained. So, the equity and need, that were declared as main principles of distribution, seem not to be observed. Moreover, the group insists that the WTP threshold

should be the subject of the political discussion and the approach can be used for some diseases until more accurate calculations arise. [93] But still the prioritization principle of the Magnussen group seems to be adequate in the CEA of the new intervention (the higher the severity – the higher maximum level of WTP threshold).

Another important issue is at what stage of liver disease the treatment is the most cost-effective. As it was shown by the results of BIA in the study, the treatment of the HCV at earlier stages (METAVIR F0) leads to fewer cases of advanced liver diseases and lower direct costs in the future. The results could be different if there was no assumption that SVR rate in patients with compensated cirrhosis (METAVIR F4) equals SVR rate in patients with mild and moderate stages of fibrosis (METAVIR F1-F3) as many studies and meta-analysis prove higher health outcomes and lower HCV-related mortality rates in non-cirrhotic patients compared with cirrhotic patients. [90, 94, 95] Thus, the total cost of care associated with advanced liver disease could be reduced in case if the treatment is initiated at early stages of liver disease: the number of cases of advanced liver disease in therapy with DAAs at early stages almost zero whereas in therapy at moderate stages of fibrosis (METAVIR F2-F3) and compensated cirrhosis (METAVIR F4) around 450 of DC, 202 – of liver cancer and 37 – of liver transplantation during the life-time among 1000 patients observed. This can be the argument for the early diagnostics across all categories of people that are or were under risk of transmission of HCV.

The limitation of the study is that the number of comparators was limited – only two whereas around 11 DAAs authorized in Norway and used in the anti-HCV therapy, so the results of the analysis can be considered unrepresentative or EBR/GRZ and LDV/SOF could be less cost-effective. But still these two DAAs have higher SVR rates in patients of genotype 1 and prescribed by Norwegian guidelines, lead to lower costs and associated with lower adverse events (though AEs are not serious among all DAAs). And EBR/GRZ is still very new (authorized in 2017) and was expensive in the beginning. As the price was reduced, the cost-effectiveness of EBR/GRZ seems to be more obvious, but the additional analysis is necessary for clinicians and decision makers to know better the health outcomes and possible harms in the long-term that is the main goal of CUA. The results can be interesting for representatives of other hospitals in Norway and abroad that use pegIFN/RBV for treatment of genotype 1 HCV infected patients. Though the old standard technology is suggested very effective in patients with genotype 2 and 3 HCV infection under age of 40 y.o.

Another limitation is uncertainty of the transition probabilities and utility weights. To achieve the goal of this study the model was based on the estimates from the natural liver disease

progression data found in the literature. Thus, the disease progression is assumed to be the same for all treatment strategies over the lifetime that is not always comparable with real cases. Moreover, the data from the literature and studies based on the clinical trials conducted in other countries and cannot always collate with Norwegian population. For instance, age- and health state-based utilities were taken from the American survey that used the evaluations of the American population aged 20-80 and older that eventually differ from Norwegian on demographic, individual and risk factors. But such kind of information is hardly accessible in every country, nonetheless it is important to use in CUA the data received from the clinical trials with representative population to follow the rule of heterogeneity.

The third limitation is that the effect of SVR on the transmission rates wasn't considered, though the inclusion could lead to more favourable results.

Fourth, the model is considering only the direct costs, neglecting the possible losses connected to the disease, for example, the omission of the productivity loss. The study is also considering only the mono-infected patients, whereas in life HCV infected patients often have coinfections such as HBV, HIV, kidney disease or diabetes; comorbidities, alcohol addiction or other individual characteristics creating the higher risk of the disease progression. That could be explained that the patient-level data, provided by Akershus university hospital, included very limited number of patients with such risk factors detected together with HCV. For this reason, these factors were neglected. Nonetheless, the treatment of HCV infected patients with coinfections and comorbidities should be studied additionally as such cases associate at times with higher fibrosis progression, at times lower SVR rates and more severe adverse events, but sometimes get higher health benefits then HCV mono-infected patients.

There are also many arguments that the real-world number of patients completed the treatment and achieved SVR rates is lower than the inputs from the studies and CT. Therefore, the inputs on efficacy of the treatment can stay very robust despite the standard deviation of 10% used in the probabilistic analysis, providing the individual heterogeneity in chronic HCV progression.

The limitation relates to the insufficient description of adverse events in the model. It is considered that the patients face the adverse events more often than it is presupposed in the study. It should be studied additionally, but still it is very difficult to assess the grade at which the disease or therapy impacts the health state and perception of utility/disutility of the intervention for health. Therefore, the utility/disutility values can be considered very uncertain.

One more limitation arises from the cases of successful and unsuccessful treatment. From one side, SVR achievers can be re-infected and the accumulated health outcomes can be considered overestimated. The probability of reinfection is reflected in the study, so the overestimation is less possible. From another side, the treatment for non-responders can be still beneficiary that is not considered in the model.

The data on resource use can be insufficient. The cost of HCV care and adverse effects were hardly accessible as it is complicated to assess even for clinical experts and personnel the costs associated with every patient or health state. The information on all DRGs relating to HCV, in- and outpatient care was extracted from national and international reports and guidelines. And still the inputs can be unexhaustive for real-world assessment of the economic outcomes of the treatment. Since the data from number of sources can be different, I relied on the sources that correspond the most the perspective and the population. The cost of the future therapy is unknow in most of the cases. And the model cannot catch the possible price reduction of the drugs that can influence the cost-effectiveness. The price is supposed to have been be reduced from March 2017, consequently, it is possible to conclude that the lower price makes the therapy even more cost-effective, available for bigger number of patients, or the Norwegian government can choose to treat HCV infected patients for less money, making possible the treatment of other diseases of a high priority.

The limitation also goes from the so-called "memoryless" property of the state-transition model characterized by that the transition probability of shifting from the current health state to the next one depends on the current state and omits the history status. It would be fair to assume that "non-responders" to the current treatment (those who stay in a health state without reaching SVR) can be "non-responders" to another treatment, and the probability of disease progression is higher in their case. Unfortunately, the model has no memory and the transition probabilities are the same for all patients in the same health state without considering the previous history of the disease and treatment.

The parameter uncertainty was studied in frames of PSA, but the structure of the model can be another source of uncertainty as many assumptions were made, and the appropriateness of these assumptions as well as the results can be debated. The Markov model includes 13 health states, so it is a complimentary model, meaning that big number of health states makes the model less transparent and the results of the model less accurate. It was possible to see that only a few health states were accumulating most of the patients. But from another point of view,

excluding some health states would lead to loss of the information on patients and disease progression.

7 Conclusion

This study was prompted by the need of Akerhus University Hospital to evaluate the cost-effectiveness of new DAA-based anti-HCV treatment with old price regime. To do this a model was conducted to compare three treatment strategies in a Norwegian context and to evaluate the outcomes in a life-time horizon. Those strategies are: 48-weeks therapy with old standard combination of pegIFN and RBV; 12-weeks DAA-based therapy with EBR/GRZ (Zepatier); 12-weeks DAA-based therapy with LDV/SOF (Harvoni). In March 2017 the new price regime on DAAs, including EBR/GRZ and LDV/SOF, was achieved by efforts of LIS. After that it is presupposed that DAAs are getting cost-effective, whereas the "pre-rebate" period keeps the questions on the long-term health and economic outcomes of this new treatment regimes. As the new prices are not available, still BIA, EVPI of the treatment with EBR/GRZ were conducted for old price and assumed 40%-rebated price to show the possible development of cost-effectiveness of the new drug as a result of the price reduction.

The new generation of DAAs such as EBR/GRZ and LDV/SOF are associated with short treatment length, substantially higher SVR, safety profile and higher chances to get rid of the HCV for all interferon-intolerant patients leading to the improvements in patients' outcomes and positive treatment experience. All these facts were found by Akershus university hospital that launched DAA-based treatment in practice in 2014, but still had no exact assessment of cost-effectiveness of these pegIFN-free treatment strategies. This study was prompted by the need of Akerhus University Hospital to evaluate the cost-effectiveness of new DAA-based anti-HCV treatment. In March 2017 the new price regime on DAAs, including EBR/GRZ and LDV/SOF, was achieved by efforts of LIS. The subject of interest is "pre-rebate" time from March 2014 till March 2017 when DAAs were provided by manufacturers for full price, so that the novel treatment of HCV was associated with high costs and its cost-effectiveness was debated. The main goal was to assess the long-term economic and health effects of the DAAs in patients that were treated with DAAs during 2014-2017. To do this a model was conducted to compare three treatment strategies in a Norwegian context and to evaluate the outcomes in a life-time horizon. Those strategies are: 48-weeks therapy with old standard combination of pegIFN and RBV; 12-weeks DAA-based therapy with EBR/GRZ (Zepatier); 12-weeks DAA-based therapy with LDV/SOF (Harvoni).

The results of deterministic and probabilistic analysis demonstrated that these two regimens could be cost-effective in comparison with pegIFN/RBV. To be more precise,

EBR/GRZ is optimal than LDV/SOF as it gave the same number of QALYs gained (16.6) for not significantly but smaller costs (1 747 748 NOK per patient vs. 1 882 326 NOK per patient respectively) that corresponds the ICER for 716 158 NOK per additional QALY gained by EBR/GRZ and ICER of 841 727 NOK per QALY gained by LDV/SOF.

And both regimens were found cost-effective at WTP-threshold 700 000 NOK by the probabilistic analysis compared with pegIFN/RBV-based therapy: 13.94 QALYs (per patient) with mean costs 2 176 740 NOK (per patient) for therapy with EBR/GRZ and 13.94 QALYs (per patient) with mean costs 2 313 831 NOK (per patient) for therapy with LDV/SOF. But if WTP-threshold is lower (e.g. 500 000 NOK) the cost-effectiveness of LDV/SOF is under the question. Both treatment strategies were compared with old standard therapy. However, the findings from the previous studies have shown that both regimens are cost-effective options in patients with all levels of treatment experience. [5, 90] Moreover, there is a study [57] that has shown economic dominance of EBR/GRZ versus LDV/SOF in different patient population that was partly proven by the current study as well: with almost the same QALYs the higher costs are associated with LDV/SOF. Probably, the results of CEA of EBR/GRZ could be different if there were no assumptions and limitations, but that requires additional studies.

The issue of timing of treatment is still widely discussed. To show the favorable effects of the early treatment there was an additional analysis part conducted in frames of BIA to demonstrate the budget impact of the postponed treatment. The results show the higher costs of early treatment were mostly lower than postponed therapy and both treatment costs and generally significantly decreasing costs in subsequent years. But still the health and economic outcomes of the early treatment should be studied additionally to show the effects in a long perspective.

The new price regime of DAAs improves the cost-effectiveness of pegIFN-free treatment and increases its affordability and access.

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Appendices

Appendix 1. Base case transition probabilities of the HCV mono-infected patients

Parameters	Probability	Range	Distribution	Source
Fibrosis progression				
F0 to F1	0.117	0.1053 – 0.1287	Dirichlet	[18]
F1 to F2	0.085	0.0765 – 0.0935	Dirichlet	
F2 to F3	0.12	0.108 – 0.132	Dirichlet	
F3 to F4 (CC)	0.116	0.1044 – 0.1276	Dirichlet	
Reinfection				
SVR F0-F3 to F0-F3	0.047	0.423 – 0.0517	Dirichlet	[57]
SVR F4 to F4	0.047	0.423 – 0.0517	Dirichlet	[57]
Cirrhosis progression				
F4 to DC	0.029	0.018 – 0.022	Dirichlet	[57]
F4 to HCC	0.028	0.0252 – 0.0308	Dirichlet	
SVR F4 to DC	0.008	0.0072 – 0.0088	Dirichlet	[74]
SVR F4 to HCC	0.005	0.0045 – 0.0055	Dirichlet	[75, 76]
DC to HCC	0.068	0.0612 – 0.0748	Dirichlet	[77]
DC to LT	0.023	0.0207 – 0.0253	Dirichlet	[78-80]
HCC to LT	0.04	0.036 – 0.044	Dirichlet	
Probability of liver-related death				
DC to liver-related death	0.126	0.1134 – 0.1386	Dirichlet	[77, 81]
HCC to liver-related death	0.427	0.3843 – 0.4697	Dirichlet	[77, 81]
LT to liver-related death	0.166	0.1494 – 0.1826	Beta	[82]
PLT to liver-related death	0.044	0.0396 – 0.0484	Dirichlet	

No fibrosis (F0), Portal fibrosis without septa (F1), portal fibrosis with new septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis (DC), liver cancer or hepatocellular carcinoma (HCC), Liver transplant (LT), post-liver transplant or subsequent years (PLT), liver-related death (LV-death), death from all other causes (All-cause death), sustained virologic response (SVR)

Appendix 2. Cost information, estimated average number of consultations, admissions and lab packages, depending on stage of the liver disease. Based on published literature and conversations with experts and the information from the available sources. [47]

	Health state							
Unit of costs	**F0-F1**	**F2-F3**	**F4**	**DC**	**HCC**	**LT**	**PLT**	**SVR F4**
GP	4.5	4.5	5.5	5.5	5	10	18	2
Clinical consultations								
DRG 907A	4.5	4.5	10					
DRG 856G					12			
DRG 907O				9		10	2.5	
Hospitalizations								
DRG 199					1			
DRG 202				3.5		1	2	
DRG 203					2			
DRG 480						1		
DRG 480O						1		
Laborytory test								
Test with RNA	2	3	5	2	2	1	1	1
Test w/o RNA		3	5	5	5	1	1	1
Ultras. Of bile ways			1	1				
Gastroendoscopy			0.5	0.5				
Ascites-tapping				0.5				

Appendix 3. Unit costs.

	DRG-weight *	Price, NOK	Comments	Reference
GP (General practitioner)		335,00	Consultation NOK 142 (2 ad), additionally to general practitioner NOK 91 (2 dd), capitation fee (takes 4 consultations per year per patient NOK 407/4)	[73]
Clinical consultations				
DRG 907A	0.037	1 510	Clinical consultation regarding hepatitis and other non-malignant liver disorders	
DRG 856G	0.190	7 750	Clinical drug treatment of liver, biliary and pancreatic cancer	
DRG 907O	0.067	2 730	Clinical consultation regarding other diseases of liver and bile ducts	
Hospitalizations				
DRG 199	3.777	154000	Diagnosis on the liver / bile ducts / pancreas with malignant tumor	
DRG 202	1.533	62 503	Cirrhosis and alcoholic liver disease	
DRG 203	1.218	49 660	Malignant tumors in the liver / bile ducts & pancreas	
DRG 480	26.315	1 072 915	Liver transplantation	
DRG 480O	13.158	536 478	Liver transplantation, in/patient surgical treatment	
Ultrasound of bile ducts		135		
DRG 711O	0.038	1 550	Gastroendoscopy	
DRG806P	0.044	1 794	Gastroenterological abdominal procedure	
Laboratory tests				
Test with RNA		2 368		-
Test w/o RNA		60		-

Appendix 4. Costs per lab-test (NOK) [71]

Type of test	**HELFO**	**Estimated costs**	**Codes**	**Lab-package with RNA**	**Lab-package with RNA**
HCV AB[4]	22	55	704e	55	
HCV RNA PCR, qualitativ[5]	390	975	701 b,c,e,g	975	
HCV RNA PCR[6]	390	975	701 b,c,e,g	975	
HCV Ig RecomLine[7]	121	302,5	704q	302,5	
ASAT[8]	4	10	707a	10	10
ALAT[9]	4	10	707a	10	10
INR[10]	4	10	707a	10	10
Bilirubin[11]	4	10	707a	10	10
Albumin[12]	4	10	707a	10	10
Blod plateletes[13]	4	10	707a	10	10
TOTAL				2 368	60

[4] The most common test for HCV looks for antibodies in the blood that are produced in response to an HCV infection

[5] HCV-RNA qualitative test confirms active HCV infection at trial time

[6] HCV RNA PCR quantitative test - measures the amount of hepatitis C virus in the blood

[7] Strip-Immunoassay with antigens produced by recombinant techniques for the detection of IgG antibodies against HCV

[8] AST (Aspartate amino transferase) Determined to assess the degree of liver disease

[9] ALT (Alanine amino transferase) Determined to assess the degree of liver disease

[10] International normalized ratio (INR) is blood-clotting test. It is a test used to measure how quickly your blood forms a clot, compared with normal clotting time.

[11] Bilirubin is a yellowish substance that is created by the breakdown (destruction) of hemoglobin, a major component of red blood cells.

[12] Albumin is a protein made by the liver. Albumin prevents fluid from leaking out of blood vessels into tissues.

[13] Platelets are cells that help the blood to form clots. The platelet number or "platelet count" in the blood is measured as part of the complete blood count (CBC).

Appendix 5. Treatment unit costs.

Therapy	Drug	Cost per pack (NOK)	Unit dose	Quantity per pack	Recommended dose	Weekly cost (NOK)	Source
DAA treatment							
EBR/GZR	Zepatier ©	172 010	100/50 mg	28	100/50 per day (1 tablet)	43 002	Felleskatalogen
LDV/SOF	Harvoni	176 781	90 mg/400 mg	28	90/400 per day (1 tablet)	44 195	
Old standard treatment							
RBV	Ribavirin	2 937	200 mg	112	1000 mg for body weight ≤75 kg (assumed)	867	Felleskatalogen
PEG-INFalfa 2a	Pegasys	8 226	180 mg	4*180 mg	180 mg per week	8 226	