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PSYCHOLOGICAL SYMPTOMS OF THE HEPATITIS C VIRUS AND PEGYLATED INTERFERON PLUS RIBAVIRIN AND BOCEPREVIR-BASED TRIPLE THERAPIES

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A thesis submitted in fulfilment of the requirements for the degree of Doctor in Philosophy in the Department of Psychological Medicine Faculty of Medical and Health Sciences.

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Abstract

**Background and Aims:** Pegylated interferon plus ribavirin (PEG IFN + RBV) and boceprevir-based triple therapy (triple therapy) are used to treat the hepatitis C virus (HCV) and are associated with psychological symptom severity, decreased quality of life (QOL), increased fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive dysfunction, and treatment satisfaction. While PEG IFN + RBV and triple therapies are still in use it is relevant to research psychological symptoms and clinical outcomes to assess and quantify the impact of those therapies. The aim of the study was to determine at treatment end and at three-month follow-up the psychological symptoms of the PEG IFN + RBV therapy and triple therapy.

**Methods:** Sixty-five patients presenting for PEG IFN + RBV therapy (30 patients) and triple therapy (35 patients) were evaluated at treatment initiation (baseline), treatment end and 3-month follow-up to treatment end. At each evaluation patients completed the Quality of Life Inventory (QOLI), Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Inventory (PSQI), Hospital Anxiety and Depression Scale (HADS), Addenbrooke’s Cognitive Evaluation-Revised (ACE-R), Trail Making Test-A and B (TMT-A and B) and the Patient Satisfaction Questionnaire-18 (PSQ-18).

**Results:** For both therapies, and for all psychological symptoms measured in the study, both patients achieving sustained virological response (SVR) and non-responders on average reported impaired baseline mean scores when compared to normative means and at treatment end all mean scores indicated a significant impairment compared to baseline mean scores. However, in all cases, patients reported less psychological impairment at three-month follow-up compared to treatment end. Additionally, there were significant impairments from baseline mean scores to three-month follow-up mean scores in both therapies for QOL and
fatigue. In the triple therapy study the sleep disorder mean score on average at three-month follow-up was significantly more impaired than the baseline mean score. In the PEG IFN + RBV study the sleep disorder mean score on average at three-month follow-up was more impaired than the baseline mean score but the difference was not significant.

**Conclusions:** At the end of treatment with PEG IFN + RBV therapy and triple therapy both patients who achieve SVR and non-responders report significant psychological impairment including decreased QOL and increased fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive dysfunction and treatment dissatisfaction. For both therapies and for both patients achieving SVR and non-responders, all of the psychological impairments decrease from treatment end to three-month follow-up after treatment end, but all mean scores at three-month follow-up after treatment end remain above the norms of the psychological measures used in the study. From baseline to three-month follow-up for both therapies QOL and fatigue were significantly impaired. For triple therapy from baseline to three-month follow-up sleep disorders were more impaired.
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# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Diseases</td>
</tr>
<tr>
<td>ACE</td>
<td>Addenbrooke’s Cognitive Examination</td>
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<tr>
<td>ACE-R</td>
<td>Addenbrooke’s Cognitive Examination-Revised</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>APA</td>
<td>American Psychological Association</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>BFI</td>
<td>Brief Fatigue Inventory</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CBT</td>
<td>Cognitive Behaviour Therapy</td>
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<tr>
<td>CFIDS</td>
<td>Chronic fatigue immune dysfunction syndrome</td>
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<tr>
<td>CFS</td>
<td>Chronic Fatigue Syndrome</td>
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<td>CHC</td>
<td>Chronic Hepatitis C</td>
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<td>CLDQ</td>
<td>Chronic Liver Disease Questionnaire</td>
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<tr>
<td>CNS</td>
<td>Central nervous system.</td>
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<td>DAA</td>
<td>Direct acting antiviral</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of Liver Disease</td>
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<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
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<td>EVR</td>
<td>Early virological response</td>
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<tr>
<td>FDA</td>
<td>The American Food and Drug Administration Agency</td>
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<td>FIS</td>
<td>Fatigue Impact Scale</td>
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<td>FSS</td>
<td>Fatigue Severity Scale</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>HA</td>
<td>Haemolytic anaemia</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
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<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HE</td>
<td>Hepatic encephalopathy</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HRQL</td>
<td>Health Related Quality of Life</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<td>IU</td>
<td>International Unit</td>
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<tr>
<td>LDV</td>
<td>Ledipasvir</td>
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<tr>
<td>LFT</td>
<td>Liver function test</td>
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<tr>
<td>MBSR</td>
<td>Mindfulness-based stress reduction</td>
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<tr>
<td>MCS</td>
<td>Mental Component Summary</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<td>MS</td>
<td>Multiple Sclerosis</td>
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<tr>
<td>NART</td>
<td>National Adult Reading Test</td>
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<tr>
<td>NDDIC</td>
<td>National Digestive Diseases Information Clearinghouse</td>
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</table>
OSA(S)  Obstructive sleep apnea (syndrome)
PBC   Primary biliary cirrhosis
PCR   Polymerase chain reaction
PCS   Physical Component Summary
PEG   Polyethylene glycol
PHARMAC Pharmaceutical Management Agency
PSQ   Patient Satisfaction Questionnaire
PSQI  Pittsburgh Sleep Quality Index
QOL   Quality of life
QOLI  Quality of Life Inventory
RBV   Ribavirin
RLS   Restless leg syndrome
RNA   Ribonucleic acid
RVR   Rapid virological response
SDS   Zung Self-Rating Depression Scale
SF-36  Short Form -36
SLE   Systemic Lupus Erythematosus
SMV   Simeprevir
SOF   Sofosbuvir
SPRINT Serine Protease Inhibitor Therapy
STAI  State-trait anxiety inventory
SVR   Sustained virological response
SVR12 Sustained virological response for 12 weeks after end of treatment
SVR24 Sustained virological response for 24 weeks after end of treatment
TAP   Test for Attentional Performance
TNT   Trail Making Tests
WAIS  Wechsler Adult Intelligence Scale
WHO   World Health Organization
WHOQOL-BREF World Health Organization Quality of Life- BREF
Glossary of Terms

Actigraphy
A small device worn on the non-dominant hand which measures motor activity of the patient.

Acute infection
Any infection characterised by signs and symptoms that last for a short period of time less than 6 months. Acute infection with hepatitis C is often very mild and goes unnoticed by most people. Acute does not relate to the severity of the disease.

Alanine aminotransferase (ALT)
A protein found in the blood. When found in elevated quantities, generally indicates liver damage.

Albumins
Family of globular proteins. Most common albumins are serum albumins. The main function of serum albumin is to regulate the colloidal osmotic pressure of the blood.

Anaemia
A decrease in the amount of red blood cells or haemoglobin in the blood. This results in less oxygen in the bloodstream than a body requires.

Ascites
Accumulation of fluid in the abdominal cavity.

Aspartate aminotransferase (AST)
An enzyme found mainly in the liver bile ducts.

Asterixis
A tremor in the hand when the wrist is extended. Characterised by the inability to maintain a position.

Arthralgia
Joint pain but without inflammation of the joints that is associated with arthritis.

Autoimmune hepatitis
A chronic disease in which the body’s immune system attacks the normal components or cells of the liver and causes inflammation and liver damage.

Bilirubin
An endogenous compound. Serves as a diagnostic marker of liver and blood disorder.
Carcinoma
A form of cancer. A malignant new growth made up of epithelial cells tending to infiltrate surrounding tissues and to give rise to metastasis.

Chronic infection
An infection that is ongoing for more than 6 months. Chronic does not refer to the severity of the disease.

Circadian Rhythm
The physiological process that follows a 24-hour cycle.

Cirrhosis
Cirrhosis of the liver is a result of chronic liver disease characterised by the replacement of liver tissue by fibrotic scar tissue, leading to progressive loss of liver function. It is estimated that about 2% of persons with hepatitis C develop cirrhosis.

Clinical trials
Research procedures that test the safety and efficacy of experimental medicines on groups of people.

Cohort
Any designated group of people who are followed over a period of time and from whom data is collected.

Colostrum
A form of milk produced by the mammary glands.

Cotton wool spots
Abnormal finding on funduscopic exam of the retina. They appear as fluffy white patches on the retina.

Decompensated cirrhosis
The development of jaundice, ascites, variceal, haemorrhage or hepatic encephalopathy.

Dysgeusia
Distortion of the sense of taste.

Early virological response (EVR)
Negative HCV RNA or greater than 2 log (i.e.99%) reduction from baseline of HCV RNA in first 12 weeks of treatment.
Excessive daytime sleepiness (EDS)
The inability to maintain wakefulness and alertness during the major waking episodes of the
day, with sleep occurring unintentionally or at inappropriate times almost daily for at least 3
months.

Encephalitis
Inflammation of the brain caused by infection or an allergic reaction.

Epithelium
The tissue forming the outer layer of the body surface and lining many hollow structures.

Extrahepatic (manifestations)
Occurring in organs other than the liver (diseases or conditions that affect organs).

Fibrous
Containing, consisting or resembling fibres; the portion of a bilaminar membrane that
provides strength due to its collagen fibre content.

Fibrosis
Formation or development of excess fibrous connective tissue to replace normal tissue lost
through injury or infection.

Fibrogenesis
The synthesis of fibrous tissue. Abnormal accumulation of fibrous tissue

Flavivirus
A genus of viruses in the family Flaviviridae. This genus includes viruses which may cause
encephalitis.

Genotype
Term used to describe genetic structure of hepatitis C. There are believed to be six major
genotypes (1-6).

Gynaecomastia
Increase in breast gland size in men that is not cancerous.

Haemolytic anaemia (HA)
Form of anaemia due to loss of haemoglobin from red blood cells. In the case of hepatitis C,
HA can occur in response to the use of anti-viral drugs, in particular ribavirin.

Hepatic
Relating to the liver.
Hepatitis
A general term meaning inflammation of the liver, usually caused by viral infection.

Hepatic encephalopathy
A spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after, exclusion of brain disease, characterised by personality changes, intellectual impairment and a depressed level of consciousness.

Hepatocellular carcinoma (HCC)
Primary liver cancer.

Interferons (IFNs)
A group of signalling proteins naturally produced by the body in response to the presence of viruses, bacteria, parasites and tumour cells. The administration of synthetically manufactured interferon in large doses can help to reduce the amount of HCV in the blood and slow down or stop the disease process.

Ipsative
A descriptor used to indicate a specific type of measure in which respondents compare 2 or more desirable options and pick the one that is most preferred.

Ketoamide
Ketoacids are organic compounds that contain carboxylic acid group and a ketone group. They are involved in the Krebs citric acid cycle and in glycolysis. Ketoamide refers to the amide of a ketoacid.

Leptin
A peptide hormone that regulates food intake and energy expenditure.

Log
A log measures the changes in hepatitis C viral load. Each log corresponds to a factor of 10. A 1-log reduction means that the baseline viral load reduced by 10 times. A 2-log reduction means a 100 times reduction etc.

Metastasis
The spreading of a disease organism, especially cancer cells, from one part of the body to another.

Mindfulness
A mental state achieved by focusing one’s awareness on the present moment, while calmly acknowledging and accepting one’s feelings, thoughts and bodily sensations.
Myalgia
Pain in a muscle or group of muscles.

Negative affect
Personality variable that involves the experience of negative emotions and poor self-concept. It subsumes a number a variety of negative emotions, including anger, contempt, disgust, guilt fear, and nervousness.

Neuropathy
Disease or dysfunction of one or more peripheral nerves, typically causing numbness or weakness.

Neutropenia
An abnormally low count of neutrophils (type of white blood cell that helps protect body from bacterial infection), leading to increased susceptibility to infection.

Neurovegetative (symptoms of depression)
Symptoms leading to dissociation from society as a whole. Symptoms include physical, emotional and cognitive changes.

Nucleoside polymerase inhibitors (NPIs)
NPIs are analogues (compounds with a molecular structure closely similar to that of another) of natural substances that bind the active site of NS5B (viral protein found in HCV) and terminate viral RNA chain generation.

Ocular
Of or connected with eyes or vision.

Ophthalmologic
Related to the health of eyes and their surrounding tissues.

Palmar erythema
Reddening of palms at the thenar and hypothenar eminences.

Papilloedema
Optic disc swelling caused by increased intracranial pressure.

Paraesthesia
An abnormal sensation, normally tingling or pricking, caused primarily by pressure on or damage to peripheral nerves.
**Parenterally**
Physiology located outside the digestive tract / By some route other than through alimentary canal.

**Parotid**
Situated near the ear.

**Pegylated interferon**
Pegylated interferon is interferon with the addition of a polyethylene glycol molecule which has the effect of the drug staying in the body for a longer period.

**Perinatal**
Pertaining to the period immediately before and after birth.

**Primary biliary cirrhosis (PBC)**
A disease in which the bile ducts in the liver are destroyed.

**Primary sclerosing cholangitis (PSC)**
A disease of the bile ducts that causes inflammation and scarring within the bile ducts. Scarring makes the ducts hard and narrow and gradually causes serious liver damage.

**Protease**
Any enzyme that performs proteolysis (the breakdown of proteins into smaller polypeptides or amino acids).

**Protease inhibitors**
Class of antiviral drug widely used to treat hepatitis caused by hepatitis c virus (HCV). They prevent viral replication selectively binding to viral proteases and blocking proteolytic cleavage of protein precursors that are necessary for the production of infectious viral particles.

**Pruritus**
Severe itching of the skin.

**Psoriasis**
A chronic, non-contagious disease characterised by inflamed lesions covered with silvery-white scabs of dead skin.

**Rapid Virological Response (RVR)**
Undetectable HCV RNA by week 4 of treatment.
Reframing
A way of viewing and experiencing events, emotions to find a more positive alternative.

Ribavirin
An anti-viral drug which activates the body’s immune system against a number of DNA and RNA viruses.

Ribonucleic acid (RNA)
A polymeric acid molecule similar to DNA but containing ribose rather than deoxyribose. The flow of genetic information is from DNA through RNA to proteins.

Sarcoidosis/Sarcoid
A disease of unknown cause that leads to inflammation. Most commonly affects the lung lymph nodes, eyes and skin.

Sequelae
A morbid condition or symptom following a disease

Serine protease
Enzymes involved in many biological processes (food digestion, blood clotting, fighting infections). They help bacteria digest material and help viruses infect cells (hepatitis C).

Sclera icterus
A condition in which the whites of the eyes become yellow, often found in persons with liver disease.

Sicca syndrome
An autoimmune disease that combines dry eyes, dry mouth and another disease of connective tissue such as rheumatoid arthritis (most common), lupus, scleroderma or polymyositis.

Sleep hygiene
A variety of different practices that are necessary to have normal quality night time sleep.

Sleep episodes
Interval of sleep that may be voluntary or involuntary.

Social anchoring
Implies a person’s inability to make independent judgements.

Somatic
Pertaining to the body (soma), as opposed to the mind (psyche).
**Somatic symptom disorder**
Group of disorders which fit the definition of physical symptoms but for which there is no physical cause and which are not attributable to another mental disorder (see DSM-V).

**Somnolence**
The state of feeling drowsy, ready to fall asleep.

**Spider naevi**
Benign vascular lesions characterised by the appearance on the skin of small red dots which radiate lines resembling a spider’s web.

**Steatosis**
The build-up of fat in the liver. Excessive fat in the liver left untreated can lead to liver failure.

**Sustained Virological Response (SVR)**
Undetectability of HCV RNA 6 month after treatment has been completed. Current research suggests that if a person has a SVR for 6 months after treatment end then there is a good chance that their response will last indefinitely. SVR 12 or (24 or 48 etc.) refers to sustained virological response at 12 weeks or (at 24 weeks or at 48 weeks etc.).

**Thrombocytopenia**
Deficiency of platelets in the blood and is sometimes associated with abnormal bleeding.

**Triple therapy**
Treatment with boceprevir and pegylated interferon plus ribavirin.

**Ultrasonography**
The use of high-frequency sound waves to image internal body structures.

**Viral load**
The volume of HCV in the blood stream usually measured by a PCR quantitative test. The result is given in the number of viral particles per ml of blood.

**Viraemia**
Rapid multiplication of viruses in the blood which is sometimes associated with symptoms.
INTRODUCTION

The hepatitis C virus (HCV) is a blood-borne communicable virus. HCV causes inflammation of the liver and can lead to liver failure and hepatocellular carcinoma (HCC) (Seeff, 2002). HCV represents a major health problem and a potential cause of morbidity and mortality in the future (Yang, Zhou, & Wong-Staal, 2009). It is estimated by the World Health Organisation (WHO) that HCV afflicts 2% to 3% of the world’s population. This represents an estimated 130-170 million persons worldwide. Approximately 500,000 people die each year from HCV related liver disease (World Health Organization, 2016). It is estimated that approximately 54,000 people in New Zealand may be living with past or present HCV infection (Gane et al., 2014). Also it is estimated less than 50% of HCV-infected New Zealanders have been diagnosed and in addition less than 10% of HCV-infected New Zealanders have accessed treatment of whom only half have been cured Gane et al. (2014). Furthermore, if there is no improvement in the current low rates of diagnosis, assessment and treatment, then the number of people presenting with life-threatening complications of liver failure and liver cancer caused by the HCV is predicted to increase threefold in New Zealand over the next two decades (Gane et al., 2014).

Besides physiological side effects, HCV infection has an adverse effect on a number of psychological factors (Crone & Gabriel, 2003). While Foster (2009) stated that in most chronic diseases physiological impairment is more pronounced the psychological impairment, there is support of the view that patients with HCV may be unexpectedly impaired in psychological health compared to their impairment in physiological functioning.

The success of HCV treatment should consider more than just physiological results; it should also include psychological outcomes. If HCV therapy is deemed to be completely successful, then post treatment the patient’s psychosocial, psychological wellbeing, and
quality of life (QOL) should also return to acceptable levels. While pegylated interferon plus ribavirin (PEG IFN + RBV) and triple therapies are still in use it is relevant to research psychological variables and clinical outcomes to assess and quantify the impact of those therapies. A review of the literature reveals little research has been conducted on HCV patients psychosocial and psychological wellbeing post PEG IFN + RBV and triple therapies. In particular, there is a limited amount of research in the prevalence of sleep disorders and fatigue, and few studies have investigated psychological outcomes post treatment with PEG IFN + RBV and triple therapies. Furthermore, to date, there has been no research related to HCV therapies which have used the Quality of Life Inventory (QOLI) to measure QOL. The QOLI identifies satisfaction and importance ratings for 16 domains to measure a patient’s QOL.

Until recently, the most effective treatment for HCV was PEG IFN + RBV (Ghany, Strader, Thomas & Seeff, 2009; Manns et al., 2001; Nelson & Zeuzem, 2009). However, this therapy has many adverse physiological and psychological side effects (Larrey, Ripault, & Pageaux, 2014). These side effects may cause non-adherence to both treatment and medication and impair the quality of life (QOL) for the HCV patient (Larrey et al., 2014). The HCV treatment success rate is defined as undetectability of HCV ribonucleic acid (RNA) 6 months after treatment has been completed and is reported as sustained virological response (SVR) (Ghany et al., 2009). The PEG IFN + RBV therapy has a SVR of between 40 to 45% among patients with HCV genotype 1 and 75% to 80% for patients with HCV genotypes 2 and 3. The accepted standard of care for PEG IFN + RBV is between 24 and 48 weeks (Ghany, Nelson, Strader, Thomas & Seeff, 2009; Manns et al., 2001).

The introduction of the boceprevir-based triple therapy (hereafter referred to as triple therapy) comprising boceprevir (a first-generation direct acting agent (DAA)) and PEG IFN + RBV increased SVR for HCV genotype 1 patients. However, triple therapy has only been
approved for patients with HCV genotype 1. Studies have shown that with triple therapy, SVR is approximately 54 to 56% for 28 weeks treatment and up to 75% for 44 weeks treatment (Bacon et al., 2011; Conjeevaram et al., 2006; Kwo et al., 2010; Lim, Tan, & Mutimer, 2014; Muir & Bornstein, 2004; Poordad et al., 2011). Triple therapy has the same side effects as PEG IFN + RBV. In many cases those side effects are more severe than in the PEG IFN + RBV therapy. Furthermore, triple therapy has the added physiological side effects of anaemia, neutropenia, thrombocytopenia, dysgeusia, gastrointestinal disturbances and rashes (Barritt & Fried, 2012; Merck, 2013; Poordad et al., 2011). In addition, drug-drug interactions restrict use, and the high pill burden and treatment complexity means compliance with triple therapy is difficult (Casey & Lee, 2013). The higher rates of adverse effects in triple therapy lessens clinical tolerance (Lim et al., 2014).

It has also been shown that HCV treatment therapies may exacerbate those psychological and psychosocial factors (Crone & Gabriel, 2003). Some of these psychological and psychosocial factors are: poorer QOL and health related quality of life (HRQL) (Younossi & Henry, 2015), fatigue (Barkhuizen et al., 1999; Terman, Levine, Terman, & Doherty, 1998), sleep disorders (M Carlson, Hilsabeck, Barakat, & Perry, 2010; De Cruz, Espiritu, Zeidler, & Wang, 2012), increased mood state disturbances (Constant et al., 2005a), increased depression (McHutchison et al., 2001; Quarantini et al., 2007; Raison et al., 2005a; Raison, Capuron, & Miller, 2005), increased anxiety (Carta et al., 2012; Erim et al., 2010; Goulding, 2001; Zignego et al., 2007), decreased cognitive function (Forton et al., 2002; Monaco, Ferrari, Gajofatto, Zanusso, & Mariotto, 2012; Solinas, Piras, & Deplano, 2015) and less patient treatment satisfaction (Balfour et al., 2004).

The American Food and Drug Administration (FDA) have recently approved a number of second generation DAAs which are interferon-free with or without ribavirin (RBV). Research has shown that second generation HCV therapies may reduce many of the
adverse side effects prevalent with PEG IFN + RBV and triple therapies (Afdhal et al., 2014; Jacobson, Gordon, & Kowdley, 2013; Kowdley et al., 2014; Lawitz & Gane, 2012; Lawitz et al., 2013; Lawitz et al., 2014; Wyles et al., 2015). On 10 August 2015 Pharmaceutical Management Agency (PHARMAC), the New Zealand government’s agency responsible for the procurement of state-funded medicines, issued a Request for Information for second generation DAAs for the treatment of HCV (PHARMAC, 2015). PHARMAC decides on behalf of District Health Boards which medicines are subsidised.

At the time of writing PHARMAC had approved funding for PEG IFN + RBV therapy, triple therapy and the DAA Viekera Pak (paritaprevir with ritonavir and ombitasvir with dasabuvir) and Viekera Pak + RB. PHARMAC funding for Viekera Pak and Viekera Pak + RBV became effective on 1 July 2016. While PEG IFN + RBV and triple therapies are still being funded and prescribed for HCV treatment in NZ it is beneficial to investigate the psychological symptoms these therapies have on patients during and post treatment. There has been much research on the psychological and psychosocial impact of HCV treatment in other countries. However, for unknown reasons, there has been little NZ research available relating to the psychological and psychosocial effects of HCV treatment in NZ. This makes the rationale for this investigation even more compelling.

The cost to PHARMAC for PEG IFN + RBV medicines for a 24 week and 48-week treatments is NZ$11,850 and NZ$23,700 respectively (see Appendix G). The cost of triple therapy medicines ranges from NZ$43,915 to NZ$78,865 (see Appendix G) depending on whether a patient is cirrhotic or non-cirrhotic and whether a patient is treatment naïve or treatment experienced (PHARMAC, 2013). In addition to the above drug costs, the total cost of treatment also includes expenses such as doctors and nurses and associated delivery costs.

This doctoral thesis is based on a health psychology biopsychosocial model. Division 38 (Health Psychology) of the American Psychological Association (APA) states health
psychology involves the scientific relations among psychological factors, behaviour and physical health and illness (American Psychological Association, 2016). It is the application of psychological theory, methods and research to health, physical illness and health care and is concerned with the psychological aspects of promotion, improvement and maintenance of health (Marks, Sykes, & McKinley, 2003). HCV infection and treatment, while having physiological affects, also have important psychological and social outcomes which validate the use of a health psychology perspective in this doctoral thesis.

Furthermore, the focus of this doctoral thesis is on PEG IFN + RBV and boceprevir based triple therapies and the differential effect over time (i.e. baseline, treatment end and three-month follow-up) that those therapies have on the effects of QOL, sleep, fatigue, mood states, depression, anxiety, cognitive function and patient satisfaction. In focusing on these changes over time it is necessary to fully investigate these effects and the demographics of the study participants at baseline. The results of the investigation will be discussed in the context of previous research. Interventions to address adverse effects of HCV and of the two therapies will also be discussed.

QOL in this thesis encompasses the domains: health, self-esteem, goals, money, work, play, learning, creativity, helping, love, friends, children, relatives, home and neighbourhood and the patients’ satisfaction and importance rating of those domains. Mood states encompasses the scales: anger/hostility, confusion/bewilderment, depression/dejection, fatigue/inertia, tension/anxiety and vigour/activity. Mood states is a measure of patient satisfaction with, and perception of the importance of, the mood state scales. It is also a measure of a patient’s positive or negative affect. The author is mindful that other topics of health psychology such as illness perception, mindfulness, benefit finding (finding positive meaning in one’s illness), positive and negative affect, positive adjustment, coping processes, non-pharmacological pain management, socioeconomic status and effects of caregivers can
pose unique challenges to HCV-infected patient. However, the measurement of those factors over time is not a focus of this thesis.

Chapter One will discuss HCV, HCV genotypes, viral load, diagnostic criteria, epidemiology, gender differences and the social stigma of hepatitis C. Chapter Two will discuss the treatments for HCV including the aim of treatment, the eligibility for treatment, and history of HCV treatment, and an explanation of PEG IFN + RBV therapy and triple therapy, DAAs, and complementary and alternative medicines. Chapter Three will discuss the literature and empirical research on HCV and health psychology, QOL, fatigue and sleep disorders, patient mood state disturbances, depression and anxiety, cognitive functioning and patient satisfaction. Chapters Four through Six will describe the study’s aims, research questions and methodology and the results of data analyses. Chapter Seven will present a discussion of the study’s findings in the context of previous studies and empirical research, the contributions and limitations of the study, general conclusions and recommendations for future research and interventions.
CHAPTER ONE
HEPATITIS C VIRUS

1.0 DEFINITION OF HEPATITIS C VIRUS

The hepatitis C virus (HCV) is a blood-borne virus that is spread through blood-to-blood contact with a person who is infected with HCV. HCV causes inflammation of the liver and can lead to liver failure and hepatocellular carcinoma (HCC) (Seeff, 2002). HCV is a single stranded, enveloped ribonucleic acid (RNA) virus belonging to the flavivirus family having one positive sense RNA genome (Sharara, Hunt, & Hamilton, 1996). Acute hepatitis C (lasting less than six month) infection is usually mild and subclinical, however there is a high incidence of progression to chronic hepatitis C after infection (Farnik, Mihm, & Zeuzem, 2009). Chronic hepatitis C is a result of an intermediate immune response which destroys hepatic cells and causes fibrosis. However, this immune response does not eradicate the virus (Poynard, Yuen, Ratziu, & Lai, 2003).

The identification of HCV has been quite recent. Hepatitis A and B were distinguished in the 1940’s. However, it was not until 1965 when the hepatitis B virus (HBV) antigen was isolated that it became known that a further virus which had previously been unidentified was causing post-transfusion hepatitis. In 1975 this unidentified virus was labelled non-A non-B hepatitis. In 1989 HCV was identified and was found to account for 85% of non-A and non-B hepatitis cases (Choo et al., 1989).

1.1 EPIDEMIOLOGY

1.1.1 PREVALENCE

World-wide it is estimated that 130-170 million persons are infected with HCV. This represents approximately 3% of the world’s population, and approximately 500,000 people die each year from hepatitis C related disease (World Health Organisation, 2015). Prevalence
of HCV infection worldwide rose from 2.3% to 2.8% between 2005 and 2009 (Modh Hanafiah, Groeger, Flaxman, & Wiersma, 2013). The prevalence of HCV infection is lower in industrialised/westernised countries such as North America, Northern and Western Europe and Australasia compared to Africa and Asia, which have the highest reported rates (Zidan, Scheuerlein, Schule, Settmacher, & Rauchfuss, 2012). For almost all countries, the peak of HCV-related cirrhosis, hepatocellular carcinoma and liver-related death is a decade or more away (Wedemeyer, Dore, & Ward, 2015).

Epidemiologic data in New Zealand is poor and an accurate number of persons infected with HCV in New Zealand are not known (Gane et al., 2014). However, it is believed that between 45,000 and 50,000 persons in New Zealand are living with chronic hepatitis C (Gane, Stedman, & Hyland, 2010). The prevalence of HCV infection in NZ peaked in 2010 with 50,480 reported cases, however peak prevalence of cirrhosis and HCC will occur in 2030. Every year in NZ, 1,000 people contract hepatitis C. Furthermore, it has been predicted that if there is no improvement in the current low rates of diagnosis, assessment and treatment, then the number of people presenting with life-threatening complications of liver failure and liver cancer caused by hepatitis C is predicted to increase threefold over the next two decades (Gane et al., 2014).

1.1.2 **MODES OF TRANSMISSION**

Hepatitis C is transmitted by blood-to-blood contact and is primarily transmitted parenterally. Infected blood must enter the bloodstream of an individual through a rupture or skin opening (Alter, 2002). The most common form of transmission is through the sharing of needles by injecting drug users (Law et al., 2003). The prevalence of HCV infection among long-term injecting drug users is between 64% - 94% (Shepard, Finelli, & Alter, 2005). HCV was also transmitted through blood transfusions prior to screening of donated blood in New Zealand on July 27th 1992 (New Zealand Haemophilia Foundation, 2004). Furthermore HCV
may be transmitted through unsterilised dental procedures (Mahboobi, Porter, Karayiannis, & Alavian, 2013), unsterilized tattooing procedures (World Health Organization, 2016) and needle-stick or other occupational exposure by healthcare workers (National Digestive Diseases Information Clearinghouse (NDDIC), 2006) although rates under these circumstances are as low as 0.3% (Shepard et al., 2005).

The role of sexual transmission is controversial and if sexual transmission does occur it is at a very low level (Vandelli et al., 2004). Sexual transmission may be increased when blood is present in the genital tract, such as during menstruation, however studies have shown sexual transmission of HCV within heterosexual monogamous couples is extremely rare or even null (Vandelli et al., 2004). The risk of transmission from sexual contact increases for those with multiple sex partners, have a sexually transmitted disease, engage in rough sex, or are infected with HIV (Centers for Disease Control and Prevention, 2016).

There is approximately a 5% risk of perinatal transmission and there is no established effective method to interrupt prenatal transmission (World Health Organization, 2016). The effect on infants of breastfeeding by HCV-infected mothers has been uncertain and variable (Gibb et al., 2000; Mast et al., 2005). However, the low odds of viraemia in exclusively breast-fed children have suggested HCV-specific immunoglobulins in colostrum and breast milk might protect against HCV transmission during infancy (Hanson & Korotkova, 2002).

1.1.3 **RISK OF CHRONIC INFECTION AND SEQUELAE OF DISEASE**

HCV is preventable. However, certain populations are at risk. Intravenous drug users are particularly at risk (World Health Organization, 2016). An Australian study reported that 80% of the 264,000 infections in 2005 were attributable to intravenous drug use and of the 9,700 new infections in that year 89% were attributable to injecting drug use (Law et al., 2003).
In addition to injecting drug users an inclusive list of the populations possibly at-risk HCV infection is:

- Individuals who have been incarcerated in prison (World Health Organization, 2016).
- Individuals who have had tattoos, acupuncture or body piercings in unsafe/unsanitary conditions (World Health Organization, 2016).
- Migrants from countries with a high prevalence of HCV (Sim, Cheng, Dore, & Beers, 2008).
- People who snort (inhalation through nose) drugs using shared inhalation implements (Macias et al., 2008; World Health Organization, 2016).
- Healthcare workers getting pricked with a needle that has infected blood on it (National Digestive Diseases Information Clearinghouse (NDDIC), 2006).
- Children born to mothers with HCV infection (World Health Organization, 2016).
- People with HIV infection (World Health Organization, 2016)
- Recipients of infected blood products or invasive procedures in healthcare facilities with inadequate infection control practices (World Health Organization, 2016).
- Recipients of unsterilised dental procedures (Mahboobi et al., 2013).

Less common risks include:

- People with sexual partners who are HCV-infected (Centers for Disease Control and Prevention, 2016; World Health Organization, 2016).
- Sharing personal care items, such as razors and toothbrushes, that may have come in contact with the blood of a HCV-infected person (Centers for Disease Control and Prevention, 2016).
1.2 DIAGNOSIS

1.2.1 EARLY DIAGNOSIS

The best treatment outcomes are for those persons who are diagnosed and treated early (Gane, 2008; World Health Organization, 2016). However, many individuals with the HCV do not experience symptoms or if they do the symptoms are sub-clinical or non-specific (Gane, 2008). Fewer than 5% of HCV-infected patients in New Zealand have received antiviral therapy due to under diagnosis or lack of resources (Gane, 2008).

Some patients diagnosed with HCV infection may have no symptoms (Gane, 2008), and therefore their QOL is not affected by physiological symptoms. Other patients may suffer significant physiological symptoms which result in devastating changes to their QOL.

Because HCV symptoms are not always evident it is recommended that persons who fit the at-risk profile to be tested for the virus. It has been suggested by clinicians that asymptomatic patients with abnormal liver function test results or elevated alanine aminotransferase (ALT) are also to be considered at-risk (Harley, Shaw, & Steven, 2003). Those individuals at-risk to HCV are discussed in this chapter under epidemiology.

Testing provides an early diagnosis of the HCV enabling patients to receive the necessary treatment before the liver is irreversibly impaired. In addition, an early diagnosis enables the patient to adopt precautions to avoid spreading the virus further and to change their lifestyle (e.g. avoidance of alcohol and drug use, maintaining a healthy diet and more regular exercise) which may reduce the progression of the liver disease to cirrhosis (Gane, 2008).

However, despite the importance of early detection, it has been reported among patients with HCV that perceived physician incompetence was a known barrier to care (Zichmund, Ho, Masuda, Ippolito, & La Brecque, 2003). Indeed a 2010 study found that
healthcare professionals have demonstrated key knowledge deficits related to HCV risk factors, prevention, management and prevalence (Mitchell, Colvin, & Palmer Beasley, 2010).

A 2001 national survey of the management of HCV patients by primary care physicians in the USA reported 73% of respondents reported seeing 5 or fewer HCV patients in the preceding year. Of the respondents 44% reported no experience with HCV treatment (Shehab, Sonnad, & Lok, 2001). Furthermore, it has been reported that although most physicians correctly identified risk factors for HCV, only 59% reported regularly screening for HCV risk factors (Boaz, Fiore, Schrag, Gonik, & Schulkin, 2003; Ferrante, Winston, Chen, & de la Torre, 2008)

Finally, 2008 United Kingdom survey of General Practitioners (GPs) found that a hindrance to diagnosis and treatment was the attitude and knowledge that doctors had in relation to HCV-infected patients (Healthcare., 2008). This survey indicated that over a third of doctors in general practice were unable to read their patient’s HCV results. Furthermore, it was reported that 32% of GPs did not actually follow up patients who had tested positive for the HCV. In addition, over 67% of GPs in the survey expressed the opinion that infectious diseases did not pose a threat to public health (Healthcare., 2008). A similar survey of New Zealand GPs has not been conducted but this survey does highlight the responsibility that GPs have to ensure that patients with HCV are not left undiagnosed.

1.2.2  HCV SYMPTOMS, EXTRAHEPATIC MANIFESTATIONS AND CLINICAL EXAMINATION

The symptoms of HCV infection may not be present in some patients. However, where symptoms are present they may include fatigue, physical liver pain, nausea, loss of appetite and joint, muscle pains and yellowing of the eyes and skin (National Digestive Diseases Information Clearinghouse (NDDIC), 2006).
Usually patients complain more about extrahepatic symptoms such as fatigue and myalgia that affect QOL, than hepatic symptoms which may occur in the later stages of HCV progression (El-Serag, Kunik, Richardson, & Rabeneck, 2002; Gumber & Chopra, 1995). A study of extrahepatic manifestations of HCV found 74% of medical workers with HCV infection demonstrated extrahepatic manifestations (Cacoub et al., 1999). The Cacoub and colleagues (1999) study reported the most commonly occurring immune-related extrahepatic manifestations were: arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%) and sicca syndrome (11%). Cacoub and colleagues (2016) reported some of the inflammatory-related extrahepatic manifestations include impaired quality of life, fatigue, depression and cognitive impairment.

A clinical examination of a patient with suspected or confirmed HCV infection involves a physical examination with particular attention being paid to specific signs of chronic liver disease and associated systemic disorders. Clinicians suggest that the clinical examination include but not be limited to the general appearance and mental state of patient (Sim et al., 2008). Cacoub and colleagues (2016) also suggest that both immune-related and inflammatory-related extrahepatic manifestations should be well known by clinicians as both have an impact on the care of patients with HCV infection.

1.2.3 TESTS FOR HCV

Commonly performed tests for HCV include serological markers, virological tests, Liver Function Tests (LFT), liver ultra sound imaging and biopsies.

Serological markers

A serological marker is the first test that is recommended be performed. Results will be either antibody negative or antibody positive. Anti-HCV is detected by enzyme immunoassay (EIA). An antibody negative result indicates no contact with the virus, while a positive result shows the patient has been exposed to the virus but not whether the virus is
still present. False-positive results are occasionally a problem therefore additional or confirmatory testing is helpful.

*Virological Tests*

HCV RNA testing by a Polymerase Chain Reaction (PCR) test is carried out if the patient is antibody positive and is usually performed on the same blood sample. The test amplifies the genetic material of a virus to a level that can be detected and is used to indicate whether the patient is still infected and if so the viral load (the volume of the virus in the bloodstream) at any given time. A PCR test does not provide information on the stage of the disease. However, as the test indicates the level of viral load, it has prognostic value in determining the response to antiviral therapy.

*Liver Function Test (LFT)*

There are a number of LFTs that indicate how well the liver is functioning. An inverted aspartate aminotransferase (AST) / ALT ratio (i.e. an AST/ALT ratio of > 1.0) may indicate cirrhosis but that finding may be reversed in some patients who have cirrhosis (Sim et al., 2008).

LFTs include:

- **ALT test**: Indicates the current level of liver inflammation. ALT is a protein found in the blood and persons with elevated ALT levels are at risk of progressive liver disease (Sim et al., 2008).

- **AST test**: AST is an enzyme found mainly in the bile ducts of the liver. An AST/platelet ratio of > 1.5 is an indicator of cirrhosis.

- **Bilirubin test**: Bilirubin is an endogenous compound and serves as a diagnostic marker of liver and blood disorders. Elevated levels of bilirubin indicate cirrhosis (Fevery, 2008).
• Albumin test: A reduced albumin, in particular if combined with low platelet count, is an indicator of liver failure (Sim et al., 2008).

A limitation of LFTs is that cirrhosis may be present when ALT, AST, bilirubin and albumin are normal. One study showed that ALT level, AST level or AST: ALT ratio were not associated with HCV progression (Sinn et al., 2008).

**Xpert HCV Viral Load Test**

Visual recent study reported the Xpert HCV Viral Load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples was able to detect active HCV infection from a finger-stick sample picture (Grebely et al., 2017).

**Liver Ultrasound imaging**

Liver ultrasound imaging provides a visual picture of the liver and has been found to be useful in diagnosing HCV. A recent study reported that ultrasonographic transient elastometry alone was accurate in the diagnosis of cirrhosis and that serum indices did not add to the accuracy of test findings. It was further reported that these findings could have meant that, overall, 90% of patients correctly classified using this methodology could have avoided liver biopsy (Castera et al., 2009). Other researchers have observed that ultrasonographic transient elastometry combined with blood tests is a more effective test and could reduce the level of required liver biopsies (Cales, Boursier, & Oberti, 2009) (Boursier et al., 2008).

**Liver biopsy**

Ultrasound imaging and blood tests assist in the assessment of liver function and the presence of associated diseases that may affect decisions about treatment. It is widely recognized that the lack of HCV symptoms and a normal ALT level does not exclude progressive liver damage (Gane, 2008; Sim et al., 2008). A liver biopsy is the best reference standard to determine accurate staging and grading of the patient’s liver disease (Bedossa &
Carrat, 2009; Poynard, Benhamou, Thabut, & Ratziu, 2009; Sim et al., 2008). This test involves taking a small sample of liver tissue from the patient which can then be analysed to measure the extent of liver damage. A limitation of a liver biopsy is the invasive nature of the procedure and patients are often frightened by this aspect of a liver biopsy test (Sim et al., 2008). Poynard and colleagues (2009) state that, while they agree that liver biopsy is the best reference standard, this procedure should only be performed when all other non-invasive methods have failed.

1.2.4 SUMMARY OF DIAGNOSIS

With HCV there is a lack of correlation between a patient’s symptoms, their blood tests and the consequences that can be associated with the disease. In many instances this lack of correlation is difficult for the patient to comprehend. There are a number of tests used in the process of diagnosing HCV including anti-HCV tests, PCR tests, LFTs, ultra sounds and liver biopsies. However, an absence of symptoms, signs and abnormal ALT levels in some of these tests does not rule out the possibility of serious liver damage. Despite the invasive nature of liver biopsies this procedure is the definitive standard for the assessment of and determining the stage of the HCV (Bedossa & Carrat, 2009; Poynard, Benhamou, et al., 2009; Sim et al., 2008).

1.3 HCV GENOTYPES

One characteristic of HCV is the high genetic variability of the virus (Messina et al., 2015). The main types of HCV are classified into genotypes. There are generally 6 recognized main HCV genotypes. Two recent systematic studies reviewed the global distribution, prevalence and circulation of HCV genotypes (Messina et al., 2015; Petruzziello, Marigliano, Loquercio, Cozzolino, & Cacciapuoti, 2016). Both systematic studies reported percentage global distributions of HCV genotypes 1-6 (see Table 1.1).
Table 1.1. Messina et al., (2015) and Petruzziello et al., (2016) systematic research’s % global distribution of HCV genotypes.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>(Messina et al.,2015) %</th>
<th>(Petruzziello et al.,2016) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>46.2</td>
<td>49.1</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>17.9</td>
<td>30.1</td>
</tr>
<tr>
<td>Genotype 4,5 and 6</td>
<td>35.9</td>
<td>20.8</td>
</tr>
</tbody>
</table>

The Messina and colleagues (2015) systematic study used 1,217 studies published between 1989 and 2013 reporting HCV genotypes, covering 117 countries and combined those with overall HCV prevalence estimates from the Global Burden of Disease (GBD) project. The Petruzziello and colleagues (2016) systematic study used published data from 557 studies between 2000 and 2015 covering 138 countries and global and continental reports. Messina and colleagues (2015) and Petruzzielo and colleagues (2016) reported genotypes 1 and 3 as the most prevalent worldwide (see Table 1.1). Petruzziello and colleagues (2016) reported the reason their study reported different percentage genotype prevalence compared to the Messina and colleagues (2015) study was due to the inclusion in their study of some countries previously excluded and also due to their data being summed with other global and continental reports.

Those genotypes originating from specific geographic regions include genotype 1 (Central Africa), genotype 2 (West Africa), genotypes 3 and 6 (South and East Asia), genotype 4 (Central Africa and the Middle East) and genotype 5 (Southern Africa) (Kuiken & Simmonds, 2009; Messina et al., 2015). It is expected that further variants of HCV will be discovered and a correct classification will be dependent on whether they show any significant grouping to existing genotypes (Kuiken & Simmonds, 2009). Murphy and colleagues (2015) reported the identification of a new HCV genotype 7.
HCV genotype 1 is the most common genotype in western countries, followed by genotype 3 (Messina et al., 2015; Petruzziello et al., 2016). Over one third of genotype 1 cases are located in east Asia and three quarters of genotype 3 are located in south Asia. East Asia accounts for the greatest number of genotype 2 and 6 cases. North Africa and the Middle East have the largest number of genotype 4 and the great majority of genotype 5 cases are in southern and eastern sub-Saharan Africa (Messina et al., 2015). While genotypes 1 and 3 dominate in most countries irrespective of economic status, other genotypes, which account for a significant proportion of HCV cases, are prevalent in lower-income countries (Messina et al., 2015; Petruzziello et al., 2016). The reported % genotype prevalence in Australasia is: genotype 1 (55%), genotype 3 (36%) and genotype 2 (6.6%), (Petruzziello et al., 2016).

HCV genotype type 1 is the most prevalent genotype in New Zealand accounting for approximately 50 % of cases. Genotypes 2 and 3 comprise a further 40 to 45 % (Gane, 2008).

There appears to be contradictory findings from studies investigating whether there is a relationship between genotype and HCV disease progression. Studies have shown no relationship between genotype and HCV progression (Benvegnu et al., 1997; Han, Lee, Kim, Choe, & Kim, 1997; Yamada et al., 1994; Yotsuyanagi et al., 1995). Freeman and colleagues (2003) reported that it was unclear whether viral factors, such as virulence of the infecting viral genotype, impact on the development of HCV-related cirrhosis.

Some studies have reported a higher risk of developing hepatocellular carcinoma (HCC) for those patients infected with HCV genotype 1b than patients with other genotypes (Bruno et al., 2007; Raimondi, Bruno, Mondelli, & Maisonneuve, 2009; Roffi et al., 2001; Silini et al., 1996; Takada et al., 1996; Tanaka, Ikematsu, Hirohata, & Kashiwagi, 1996).

Finally, studies have shown that genotype influences the level of viral replication and the response to drug treatment for both non-PEG IFN treatment (McHutchison et al., 1998; Poynard et al., 1998; Sievert, 2003) and PEG IFN treatment (Fried et al., 2002; Hadziyannis
et al., 2004; Manns et al., 2001). Genotype 1 is well served by advances in non-IFN second
generation Direct Acting Agent (DAA) drug development. However, other genotypes, which
are less well served by advances in drug development, still comprise more than half of
worldwide HCV cases (Messina et al., 2015).

1.4 VIRAL LOAD

HCV viral load refers to the amount of HCV in a person’s blood (Albrecht, 2016). It
is expressed as the amount of ribonucleic acid (RNA, or genetic material) per millilitre of
blood (Hepatitis C Research and Liver Health, 2016). Viral load tests are often used before,
during and post-HCV treatment to help determine response to, and to manage therapy
(Hepatitis C Research and Liver Health, 2016).

There are two categories of HCV viral load tests (Hepatitis C Research and Liver
Health, 2016). Firstly, Qualitative viral load tests determine the existence of HCV RNA in a
person’s blood and is usually used to confirm chronic infection with HCV. A positive test
result indicates viral RNA. Secondly, quantitative viral load tests measure the amount of
virus in one millilitre of blood. A quantitative viral load test is often used to determine, pre-
treatment, whether treatment is likely to be successful during treatment; whether treatment is
being effective; and post treatment, whether there has been relapse in viral load. A
polymerase chain reaction (PCR) test is the common quantitative viral load test used to detect
HCV RNA in the blood, which indicates current active infection. A PCR test is very sensitive
and can measure as few as 50 IU/ m L (meaning if a person’s viral load is below 50 IU/ m L
then HCV could be present but would not be detected by the PCR test). There are two other
quantitative HCV viral load tests; the branched chain DNA (b DNA) test which only
measures viral loads greater than 500 IU/ m L and the transcription-mediated amplification
(TMA) test which is a newer test and can measure as few as 5-10 IU/ m L.
The results of the viral load (HCV RNA) test are usually expressed as International Units / mL (IU/ mL) (Hepatitis C Research and Liver Health, 2016). A patient with an 800,000 IU/mL is considered to have a high viral load. There is no correlation between viral load and the severity or progression of hepatitis C (Albrecht, 2016). However, a number of studies have shown that lower viral loads respond better to HCV therapy (Hepatitis C Research and Liver Health, 2016). Changes in viral load are often reported as log changes. Log changes measure changes in hepatitis C viral load by a factor of 10. Thus, if a baseline serum HCV RNA were 20,000 copies/ml plasma then a 1 log increase equals 200,000 copies /mL plasma. A 2 log increase equals 2,000,000 copies/ml plasma (that is a 100-fold increase). For example, if the baseline was 20,000 copies/ml plasma, then a 2-log reduction equals a viral load of 200 copies/ml plasma. A 1 log reduction would mean the viral load would decrease to 2,000 copies/mL plasma (Hepatitis C Research and Liver Health, 2016). The failure to achieve a viral load drop by less than 2 logs after 12 weeks of treatment is predictive of treatment failure (Anania & Pearlman, 2016).

1.5 GENDER DIFFERENCES and HCV

HCV does not discriminate against gender and both men and women are susceptible to HCV infection (Cutler, 2014). However, there are a number of factors which are gender related which are worthy of discussion. The overall prevalence of HCV infection is higher in males than in females (Butterfield et al., 2003). This is likely related to the higher prevalence of injecting drug use among men (Butterfield et al., 2003). While the transmission of HCV through sexual relations is low (Vandelli et al., 2004), females are at a higher risk of acquiring HCV from a sexual contact with an HCV-infected partner due to females having significantly higher rates of lifetime sexual risk behaviours (Butterfield et al., 2003). Female sexual risk factors include: unprotected sex in exchange for drugs, unprotected sex in exchange for money and gifts, unprotected vaginal sex and anal sex (Butterfield et al., 2003).
Females are also more likely to be initiated into drug use, share needles, or be injected by a sexual partner (Bell, Mast, Terrault, & Hutin, 2004).

Studies have shown that female patients with CHC have a lower risk than males of developing hepatocellular carcinoma (HCC) (Di Martino et al., 2004). Also women have less altered hepatic biochemical test and lower rates of fibrotic progression (Narciso-Schiavon et al., 2008). It has been reported that the lower rates of fibrotic progression are possibly related to the protective effects of oestrogen which possesses anti-fibrotic activity (Di Martino et al., 2004) and blocks fibrogenesis in the hepatic stellate cells (Yasuda, Schimizu, Shiba, & Ito, 1999).

Of those persons infected with HCV, 75-85% will develop chronic HCV infection (Centers for Disease Control and Prevention, 2016). However, 15% are able to clear the virus without medication. This is known as spontaneous clearance. Spontaneous clearance of HCV infection appears more frequent among women after acute infection. While researchers are not certain about the reason for the higher clearance rate in women, it is suspected that oestrogen’s protective properties may be responsible (Bakr et al., 2006). It is interesting to note an earlier study reported gender differences in symptom reporting disappeared at the age of 45 (Hannay, 1978).

Up to 20 percent of persons with HCV infection may develop cirrhosis (Schuppan & Afdhal, 2008). However, a 2000 study reported that only .004% of the 1018 women studied in a 20-year multicentre study developed cirrhosis (Wiese, Berr, Lafrenz, Porst, & Oesen, 2000). The female hormone oestrogen protective properties referred to above in the Bakr and colleagues (2006) study may act as a protection against liver disease making females less susceptible to cirrhosis than men.

In the general population depressive disorders are 2 times more prevalent in females (Mayo Clinic, 2016a), and anxiety disorders are also twice as prevalent in females (Anxiety
and Depression Association of America, 2016a). In a 2005 study of patients scheduled for interferon treatment for HCV it was reported depressive disorders were more prevalent in females (44%) than in males (22%), although the difference was borderline statistically significant. In the same study 24% of participants reported anxiety disorders with no gender differences. Furthermore, this study reported the prevalence of coexisting anxiety and depressive disorders was significantly higher in females (44%) compared to males (4.5%, $p = 0.012$). Finally, fatigue is a frequent and disabling symptom reported by patients with chronic HCV (Glacken, Coates, Kernohan, & Hegarty, 2003; Heeren et al., 2014; Kallman et al., 2007; Poynard et al., 2002). In a study of 78 chronic HCV patients fatigue was more pronounced in female chronic HCV patients compared to male chronic HCV patients ($p = 0.003$) (Piche et al., 2002).

Research has reported that women in the community report more intense, more numerous, and more frequent bodily symptoms than men (Barsky, Peekna, & Borus, 2001). These differences appear in samples of both medical patients and in community samples. It has been reported there are innate differences in somatic and visceral perception, differences in symptom labelling, description, and reporting, and gender bias in research and in clinical practice (Barsky et al., 2001). Barsky and colleagues (2001) summarised there were 3 factors which contributed to the differences in somatic symptom reporting between males and females. First females have a higher prevalence of anxiety and depression which themselves have prominent somatic features. Second, females have a higher rate of current and past abuse and trauma which is associated with medical help-seeking and somatic symptom reporting. Thirdly, there is a gender difference in the thresholds for judging and considering a given sensation to be obnoxious, unpleasant, and bothersome. An earlier study concluded that the differences in symptom reporting may be due to women being more willing than men to reveal distress and health problems (Nathanson, 1977). Furthermore, Delisle and colleagues
(2012) reported differences in the experience and reporting of somatic symptoms did not likely explain gender differences in depression rates and symptom severity. Interestingly, an early study reported gender differences in symptom reporting disappeared at the age of 45 (Hannay, 1978).

Differences in seeking care for HCV is another aspect of gender differences which has been investigated (Temple-Smith et al., 2007). That study reported that results suggested the impact of HCV was perceived differently by males and females. It was reported females without symptoms (47%), were more likely than males (18%) to seek care, to rate their health poorly (47% versus 35%) and to perceive discrimination from healthcare providers (47% versus 40%). In addition, males (36%) were less likely than females (6%) to acknowledge the need for medical support. Furthermore, for both genders, current injecting drug users were less to access HCV care than other populations, and male injecting drug users (18%) were less likely to be referred to a specialist than female injecting drug users (33%).

The abovementioned references highlight the complexity of the relationship between depression, anxiety, somatic symptom disorders, behaviour and gender in HCV-infected persons (Temple-Smith et al., 2007). Temple-Smith and colleagues (2007) suggested that strategies to address primary care issues for persons with HCV infection need to take into account gender differences. Finally, gender differences highlight the clinical imperative to understand the significance of each individual patient’s symptoms (Barsky et al., 2001). Gender differences relating HCV treatment and outcomes are discussed in section 2.11.

1.6 SOCIAL STIGMA OF HCV

Much has been written about the social stigma of HCV. Much of the silence and stigma around HCV comes from the myth that injecting drug use is the main method of transmission (Bruce & Montanarelli, 2013). Persons who have never been injecting drug users may find friends, family and health professionals assume a person has contracted HCV
through injecting drug use and thus those persons may find themselves being treated differently as a result (Bruce & Montanarelli, 2013). Because of social stigma, whether real or perceived, many HCV patients are embarrassed about their disease and are reluctant to divulge their illness to family, friends and acquaintances (Bruce & Montanarelli, 2013). The social stigma of HCV leads to social exclusion and isolation and impacts on the patients decisions regarding treatment uptake (Harris, 2004). Studies have shown that the stigma of HCV infection increases over time and that women report a worse quality of life than men (Strauss, 2006). Furthermore, a person with HCV infection may not be able to work or may have to work reduced hours due to the side effects of HCV. The reduction in financial resources may have a negative impact on the QOL of a person with HCV infection.

1.7 SUMMARY

The impairment of QOL for those individuals with HCV-infection is significant. The HCV is a preventable virus. However, despite the knowledge of transmission, programs such as needle exchanges and the literature available, HCV infection still remains a major health problem both in New Zealand and world-wide.

Diagnosis is difficult due to the lack of correlation between a patient’s symptoms and diagnostic tests. Because of problems with diagnoses, HCV may go undetected for some time and therefore treatment may be delayed. Early diagnosis means that treatment can be introduced at an earlier stage in the disease, resulting in a more effective therapy outcome.
CHAPTER TWO
TREATMENT OF HEPATITIS C VIRUS

2.0 INTRODUCTION

Until recently the most effective and recommended treatment of persons with HCV infection has been the combination of PEG IFN + RBV (Reddy, Nelson, & Zeuzem, 2009). This treatment has been demanding on the patient due to the many adverse side effects (Yang et al., 2009) which will be described later in this chapter. A SVR rate has been shown to be 40 to 45% among patients with HCV genotype 1 and 75 to 80% for patients with HCV genotypes 2 and 3 after 24 to 48 weeks of treatment which is the accepted standard of care for PEG IFN + RBV (Ghany et al., 2009; Manns et al., 2001; Reddy et al., 2009). PHARMAC approved the funding of PEG IFN + RBV in NZ on 1 April 2009.

Recently triple therapy, which involves a third drug, boceprevir (a protease inhibitor) in combination with PEG IFN + RBV, has been available for persons with HCV genotype 1. It has not been approved for patients infected with HCV non-1 genotype (Gane, 2012; Kwo et al., 2010). Triple therapy has been shown to increase SVR in HCV genotype 1 patients compared to PEG IFN + RBV therapy and may, depending on the patients being treated, also shorten the duration of treatment. However, triple therapy has severe side effects and therefore weak clinical tolerance (Lim et al., 2014). Furthermore, treatment failure is a significant problem with triple therapy (Bacon et al., 2011; Poordad et al., 2011). Studies have shown that with triple therapy, SVR is around 54 to 56% for 28 weeks of treatment and up to 75% for 44 weeks of treatment (Bacon et al., 2011; Conjeevaram et al., 2006; Kwo et al., 2010; Lim et al., 2014; Muir & Bornstein, 2004; Poordad et al., 2011). Triple therapy funding in NZ was approved by PHARMAC on 9 August 2013.
Because of the poor tolerability and side effects of PEG IFN +RBV and the similar, if not more severe, side effects of triple therapy, there is a need for more effective therapies which have shorter treatment time, increased SVR, more tolerability, and are effective for all genotypes. Newer classes of second generation directly acting antivirals (DAAs) have recently been developed and research continues in the further development of these drugs. The eventual aim is to eliminate interferon with or without RBV, from all HCV treatment regime (Gane, 2012).

No effective vaccines have been developed for HCV due to the fact that the hypervariable region of HCV helps it to evade the host immune response (Bukh, Miller, & Purcell, 1995). The fact that there is no vaccination available for HCV (Lavanchy, 2009), increases the need for an effective HCV therapy with higher tolerability and improved SVR (Lavanchy, 2009). In addition, risk avoidant behaviour becomes more important. Health professionals agree that the best means of HCV prevention is the avoidance of risk behaviours such as the sharing of needles by drug users (Law et al., 2003). While not curing HCV, there are life style options that may mitigate the effects of HCV such as maintaining a healthy diet, regular exercise and avoidance of heavy alcohol and drug use (Gane, 2008).

Furthermore, studies (Davis et al., 1998; Dieperink, Ho, Thuras, & Willenbring, 2003; Erim et al., 2010; Fagundes, Ferreira, & Pace, 2015; Hopwood, 2009; Kraus, Schafer, Faller, Csef, & Scheurlen, 2003; Kwo, 2012; Kwo et al., 2010; Larrey et al., 2014; Lotrich, Ferrell, Rabinovitz, & Pollock, 2009; Raison et al., 2005a; Raison et al., 2005b; Reddy, Wright, & Pockros, 2001; Thein et al., 2007; Ware, Bayliss, Mannocchia, Davis, & The Interventional Therapy Group, 1999; Younossi et al., 2014a) and anecdotal evidence from research nurses at Greenlane, Auckland Clinic, and from postings on HCV internet websites by former patients (Hep C Discussion Forum, 2016; HepForums, 2016), indicate that psychological factors have a significant effect on treatment outcomes and treatment adherence.
This chapter will discuss the treatments for HCV including treatment goals, HCV treatment in New Zealand, history and description of PEG IFN + RBV and triple therapies, second generation DAAs; FDA approved second generation DAA interferon-free trials, the European Association for the study of the liver (EASL) guidelines, the future of ribavirin, and complementary and alternative treatments.

2.1  TREATMENT GOALS

HCV is a chronic medical condition and therefore without successful treatment the physical and psychological side effects will persist and will continue to impact on a person’s QOL (Forton et al., 2002). The aim of PEG IFN + RBV therapy and triple therapy (with a protease inhibitor (boceprevir or telaprevir)), is to produce a SVR thus preventing sequelae and death from chronic liver disease (Lee & Abdo, 2003). SVR has late relapse or rates over 4-5 years, post treatment in the range of 1-2%. While some patients who achieve SVR have some regression of cirrhosis and fibrosis, they have significantly reduced risk for HCC and liver-related mortality compared to those persons who have no treatment or are non-responders to treatment (Swain et al., 2010). Furthermore, in addition to achieving SVR the purpose of any health treatment is also on the enhancement of a patient’s QOL. The emphasis of the present study is on treatment outcomes from a health psychology perspective.

2.2  HISTORICAL HCV THERAPIES

Interferon has been the main therapy for HCV infection for over 20 years. Interferons are cytokines and are the major component of the natural antiviral immune response. The cloning of human interferon brought about the possibility of treating chronic viral infections, such as HCV, with synthetic or genetically engineered interferon (Feld, 2014a). Interferon works by attaching to healthy cells to defend against the invading viruses. It assists the immune system by preventing the virus from multiplying and also assists by enabling the
body to rid itself of the infected cells but at the same time preventing healthy cells from being infected. Initial studies showed that interferon was able to suppress HCV replication and normalise liver tests in some patients (Hoofnagle et al., 1986).

The initial anti-viral interferon monotherapy for HCV produced a SVR in a low percentage of patients. Early studies involving interferon monotherapy over a 6-month period led to SVR in only 6% of treated patients. In most cases in the shorter treatment periods patients relapsed when treatment stopped (Causse et al., 1991; Poynard et al., 1996). It was later found that HCV was more likely to clear with longer treatment courses of interferons (Saracco et al., 1993; Shiffman et al., 1997).

RBV was developed in 1970 (Thomas, Ghany, & Liang, 2012) and is an effective drug against HCV when used in combination with interferon (Feld & Hoofnagle, 2005). RBV is a synthetic nucleoside analogue that possesses broad-spectrum antiviral activity against several RNA and deoxyribonucleic acid (DNA) viruses. Nucleoside analogues are man-made molecules that closely resemble the biochemical units that make up genetic material (RNA and DNA). RBV works by affecting the host response and targeting the HCV. It is immunomodulatory and enhances Th 1 CD4 responses resulting in increased activity of cytotoxic T lymphocytes and secretion of antiviral cytokines. RBV also stops viral replication by preventing the formation of the guanosine nucleoside by inhibiting inosine monophosphate dehydrogenase (IMPDH), (Abdelmalek & Davis, 2002; Hofmann, Herrmann, Sarrazin, & Zeuzem, 2008; Thomas et al., 2012). RBV has not worked well in the treatment of HCV when used alone. A 1995 study involving ribavirin showed that RBV when used alone has minor effects on the HCV RNA levels in patients with chronic HCV infection (di Bisceglie et al., 1995). However, when RBV was tested in combination with interferon-alpha it was found there were significant improvements in SVR rates (from 6-16%
Further studies have shown that IFN + RBV combination treatment was more effective than IFN plus a placebo. SVR under this RBV combination treatment ranged from 30 to 40% (McHutchison et al., 1998; Poynard et al., 1998). In addition, IFN + RBV therapy was found to be more effective than either drug alone (Buckwold, 2004). Subsequently this regime became the treatment of choice for over 10 years (Brillanti et al., 1994; Ghany et al., Strader et al., 2004).

2.3 PEGYLATED INTERFERON PLUS RIBAVIRIN (PEG IFN + RBV) THERAPY

In the late 1990’s pegylated (PEG) IFN replaced conventional IFN as the accepted standard-of-care. PEG IFN had the convenience of being administered once weekly and also had better clinical efficacy (Heathcote et al., 2000; Zeuzem et al., 2000). Pegylation refers to the process of covalent attachment of polyethylene glycol polymer chains to another molecule.

A study of patients with chronic HCV which compared PEG IFN and IFN found that the former given once weekly was more effective than the later given 3 times weekly (Zeuzem et al., 2000). Similar results were found in studies with patients suffering from chronic HCV and cirrhosis (Heathcote et al., 2000). Also pegylation has been found to confer an extended circulating life and increased drug stability and thus improves the pharmacokinetic properties of interferon (Lu et al., 2008).

As is the case with treatment involving non-PEG IFN, PEG IFN is more effective in combination with RBV. A 2003 study found that the combination PEG IFN + RBV treatment reduced liver fibrosis progression and possibly reversed cirrhosis (Poynard et al., 2003). PEG IFN + RBV studies have shown that high RBV plasma on the first day of
treatment or as measured by week four, are predictive of SVR (Loustaud-Ratti et al., 2008; Maynard, Gagnieu, Pradat, Souvignet, & Trepo, 2007). The maintenance of a high dose of RBV during treatment has also been found to be predictive of a favourable SVR (Reddy et al., 2009; Reddy et al., 2007; Shiffman et al., 2007). It has also been found that the most modifiable factor during PEG IFN + RBV combination therapy was the maintenance of an optimal RBV dose (Bain et al., 2008). Despite these findings the molecular mechanisms by which RBV improves SVR during PEG IFN + RBV therapy are still unknown (Hofmann et al., 2008).

Until recently the accepted standard of care for patients with HCV infection has been PEG IFN + RBV for between 24 and 48 weeks. For PEG IFN + RBV, SVR varies from 40-55% among patients with HCV genotype 1 and 4 and from 75-80% for patients with HCV genotype 2 and 3. (Ghany et al., 2009; Manns et al., 2001).

2.3.1 PRE-TREATMENT PREDICTORS OF PEG IFN + RBV TREATMENT OUTCOME

Predictors of treatment success (SVR) may be physiological or psychological. Studies have shown that a number of factors identify IFN-based treatment responses.

*Genotype and treatment responses*

Genotype has also been shown to be one of the two most important predictors of SVR in PEG IFN +RBV treatment, the other important predictor being pre-treatment viral load (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001). HCV genotypes 2 and 3 are more responsive to treatment compared to HCV genotype 1(Sievert, 2003). A number of studies have shown that there is a relationship between genotype and PEG IFN + RBV treatment (McHutchison et al., 1998; Poynard et al., 1998).

Gane (2008) reported that in New Zealand delivering SVR rates for HCV-infected patients treated with PEG IFN + RBV was related to genotype, with 40-55% of HCV
genotypes 1 and 4 showing a SVR and 75-80% of HCV genotypes 2 and 3 showing a SVR. Because HCV genotypes 1 and 4 are more resistant than HCV genotypes 2 and 3 to the current standard of PEG IFN + RBV treatment, it has been recommended dosage and duration of treatment be tailored to genotype (Kuiken & Simmonds, 2009; Zeuzem, 2007). The duration of Pegasys treatment for the patients who were participants of this current study was 48 weeks for HCV genotypes 1 or 4 and 24 weeks for HCV genotypes 2 or 3 as specified by PHARMAC Approval Guidelines (PHARMAC, 2009). However, the dosage of Pegasys was not tailored to genotype or any other clinical variable for the patients who were participants in this study.

**Viral load and treatment responses**

The other significant pre-treatment predictor of treatment outcome is viral load. A 2001 study of patients treated for 48 weeks with PEG IFN + RBV found that patients with a viral load of less than 2 million copies/mL had a 1.5 to 2 times better response to treatment than patients with a higher viral load (Manns et al., 2001). The Manns and colleagues (2001) findings supported an earlier study which reported pre-treatment viral load was predictive of SVR (Neumann et al., 1998). The Boulestin and colleagues (2006) study reported that a high baseline viral load showed a viral dynamic which differed from patients with a lower level of viraemia. Zeuzem and colleagues (2009) reported a baseline level of 400,000 IU/mL is the most effective cut off for a high or low probability to achieve SVR in genotype 1 HCV patients.

**Other factors and treatment responses**

Other important factors influencing treatment response but which have a lesser effect than genotype and pre-treatment viral load are: disease duration, gender, age less than 40 years, body weight less than 75kg, body surface area less than 2m square, level of liver enzymes, the absence of cirrhosis and bridging fibrosis, ALT levels greater than three times
upper limit of normal, a Knodell histological index (HAI) score greater than 10 and low hepatic iron concentration (Boulestin, Kamar, & Sandres-Saune, 2006; Fried et al., 2002; Heathcote et al., 2000; Zeuzem et al., 2000). In addition, ethnicity and insulin resistance have been found to be pre-treatment predictors of PEG IFN + RBV therapy response (Conjeevaram et al., 2007; Romero-Gomez et al., 2005).

Studies have shown that only 20% of persons who had been treated before (treatment experienced), but had not achieved SVR on initial treatment, achieved SVR on retreatment with PEG IFN + RBV. The success rate was lower for persons who did not reach undetectable levels of HCV during initial treatment (Jensen et al., 2009; Poynard, Colombo, et al., 2009; Rustgi et al., 2009; Yoshida et al., 2009).

It is to be noted that the dosage of Copegus RBV for the HCV genotypes 1 and 4 patients participating in this present study was based on whether the patient’s weight was under or over 75 kilograms and dosage for HCV genotypes 2 and 3 was not based on body weight. PEG IFN + RBV studies have also shown that high RBV plasma on the first day of treatment or as measured by week four, are predictive of SVR (Loustaud-Ratti et al., 2008; Maynard et al., 2007). The maintenance of a high dose of RBV during treatment was also predictive of a favourable SVR (Reddy et al., 2007; Shiffman et al., 2007).

2.3.2 PREDICTORS OF PEG IFN + RBV TREATMENT OUTCOME AFTER COMMENCEMENT OF TREATMENT

While pre-treatment predictors may provide a general prediction of PEG IFN + RBV therapy their accuracy in individual cases is not sufficient to make clinical decisions (Lee & Abdo, 2003). Studies have shown that both rapid virological response (RVR) and early virological response (EVR) are predictive of treatment success, RVR being a strong prediction of SVR and failure to achieve EVR being a strong prediction of non-SVR independent of patients’ pre-treatment status (Martinot-Peignoux et al., 2009). RVR is
undetectable HCV RNA by week 4 of treatment. EVR is negative HCV RNA or greater than a 2 log (i.e. 99%) reduction from baseline of HCV RNA in the first 12 weeks of treatment. Because of the side effects and high cost of PEG IFN + RBV treatment, it has been widely accepted that treatment should only be continued when SVR will be achieved (Roche, 2009a). Thus, the consideration of predictive factors in SVR is important in deciding whether to continue or discontinue treatment (Napoli, Giannelli, Antonaci, & Antonaci, 2008). The chance of identifying a virological responder correctly (positive predictive value (PPV)) range from 50 - 80%, and the chances of identifying a virological non-responders correctly (negative predictive value (NPV)) usually exceeds 90%. Therefore the decision to discontinue treatment has focused on NPV (Lee & Abdo, 2003).

An analysis of PEG IFN + RBV files indicated that using EVR would have resulted in missing a negligible number of non-responders (NPV between 98% and 99%) (Davis, 2002). The conclusion, after considering the findings of these studies, is that the decision to continue with PEG IFN + RBV treatment can be made in week 12 of treatment (Martinot-Peignoux et al., 2009). Further studies, albeit with relatively small sample sizes, have found that RVR in week 4 through to week 8 is also a strong predictor of SVR (Napoli et al., 2008) and that the inability to achieve a 85% reduction in HCV RNA after 3 days was correlated to SVR and predicted the presence of Viraemia in week 4 (Magalini et al., 2000).

PHARMAC recommend that treatment should be stopped at week 12 if serum HCV RNA level remains detectable by PCR and has not reduced by 2 logs from baseline level (PHARMAC, 2009). These guidelines are in line with the findings of studies mentioned above. PHARMAC also recommend that treatment be reduced to 24 weeks for genotypes 1, 4, 5 and 6 infections if serum HCV RNA level in the fourth week of treatment is undetectable by sensitive PCR assay (<50IU/mL) and baseline serum HCV RNA is <400,000IU/mL.
(PHARMAC, 2009). Auckland and North Shore Hospitals have advised that PHARMAC recommendations are adhered to by those hospitals.

2.3.3 SIDE EFFECTS OF PEG IFN + RBV THERAPY

While the side effects of PEG IFN + RBV are less than those of non-pegylated treatment, they are still significant (Roche, 2009b). Treatment is demanding on the patients causing depression in 15% to 60% of patients, the premature cessation of treatment in 15% of patients and the need to reduce dosage in 20-40% of patients. These are all factors that affect the outcome as adherence to PEG IFN + RBV is critical for achieving a SVR (Quarantini et al., 2007). Because of the side effects few people are able to tolerate PEG IFN + RBV treatment (Gane, 2014). Gane (2014) also stated that fewer than two per cent of those diagnosed with HCV in NZ receive treatment each year. The significant side effects of PEG IFN + RBV may contribute to a reluctance to take up treatment. The side effects of Pegasys as reported by Roche (2009b) are listed in Appendix A. The side effects of RBV are listed in Appendix B.

2.4 BOCEPREVIR-BASED TRIPLE THERAPY (PEG IFN + RBV + BOCEPREVIR)

In May 2011 the US Food and Drug Administration (FDA) approved the first two direct-acting antiviral (DAA) protease inhibitors, boceprevir (brand name VICTELIS) and telaprevir (brand name INCIVEK)) (U.S. Food & Drug Administration, 2011a). The approval was for use in combination with PEG IFN + RBV for the treatment of HCV genotype 1 infection (U.S. Food & Drug Administration, 2011a). DAAs are oral drugs which target steps of HCV replication (National Institute of Health, 2016). Both boceprevir and telaprevir target the HCV NS3/4A serine protease, making it difficult for the virus to replicate (Welsch, Jesudian, Zeuzem, & Jacobson, 2012). Boceprevir (Healthline, 2016a) and telaprevir
(Healthline, 2016b) must be used with PEG IFN + RBV to be effective. On 9 August 2013 PHARMAC approved the funding of triple therapy in NZ.

Boceprevir comes as a capsule and is taken orally (National Institute of Health, 2016). It is usually taken with a meal or small snack three times daily (every 7 to 9 hours). Triple therapy commences with a 4-week treatment of PEG IFN + RBV. The three medications (triple therapy) are then taken for 12 to 44 weeks. After this time the patient stops taking boceprevir but may continue to take PEG IFN + RBV for an additional number of weeks. The length of treatment for any patient depends on a number of factors such as the patient’s condition, whether there are side effects and how well the patient responds to the medication.

Boceprevir is a NS3 serine protease, carboxamide-based oral HCV /4a genotype 1 inhibitor (Welsch et al., 2012). In vitro studies have reported robust antiviral activity in an HCV replicon model (Malcolm et al., 2006). Malcolm and colleagues (2006) found that continuous exposure of replicon-bearing cell lines to six times the 90% effective concentration of SCH503034 (a ketoamide inhibitor) showed a more than 4-log reduction in replicon RNA by day 15. This 2006 study found that SCH503034 with interferon was more effective than either compound alone, which confirmed earlier studies which suggested that protease inhibitors combined with interferon would lead to therapeutic efficacy. The results of the Malcolm and colleagues (2006) study were the basis for designing clinical trials for boceprevir (Kwo, 2012).

Boceprevir has proven successful in phase 2 studies of both patients infected with HCV genotype 1 treatment experienced and treatment naïve patients (Berman & Kwo, 2009). Phase 2 clinical studies are conducted after a phase 1 study has proven the drug to be safe. If an experimental drug is found to be effective after a phase 2 trial the next step is a phase 3 trial. Phase 3 studies are conducted to determine if an experimental drug or treatment is more effective or has fewer side effects that the standard treatment.
A phase 2 dose-finding RESPOND-1 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and Peg Intron/Rebetrol) investigated firstly the optimal boceprevir dose to maximise SVR while minimising side effects and secondly whether RBV would be required in combination with PEG IFN and boceprevir in the treatment of null responders (Schiff et al., 2008). The study had a third goal which was to determine the optimal duration of boceprevir in the treatment of null responders. This study enrolled 357 non-responders who failed to reach EVR or who did not clear the virus after 12 weeks of therapy and who also showed an 80% adherence with medicines and duration. These patients were treated with PEG IFN and boceprevir in ascending doses of 100,200,400 and 800 mg three times a day or with PEG IFN and boceprevir 400mg three times a day and RBV. PEG IFN + RBV was received by the control arm. The investigators stated that an interim analysis by the Data Safety Monitoring Board resulted in a protocol amendment that all patients who responded (i.e. those who had <10,000 IU/ ml on their initial randomised therapy) were recommended to receive open-label PEG IFN + RBV, and 800mg boceprevir three times a week for 24 weeks. It was determined that for treatment of non-responders RBV is required for optimal response. This is also the case for patients with HCV genotype 1 infection. Finally, it was found that non-responders who at first received PEG IFN + RBV with EVR at week 13 were more likely to go on to SVR with boceprevir addition regardless of the dose.

The phase 2, HCV Serine Protease Inhibitor Therapy 1 (SPRINT-1) study evaluated boceprevir in combination with PEG IFN + RBV in HCV genotype 1 treatment-naïve patients (Kwo et al., 2010). This study involved two parts: Part one: Patients received either PEG IFN + RBV and boceprevir therapy 800mg three times a day for 28 or 48 or a lead-in strategy with 4 weeks of PEG IFN + RBV followed by boceprevir 800mg three times a day with PEG IFN + RBV for 24 and 44 weeks. These two therapies were compared with PEG IFN + RBV for 48 weeks.
Part two: Patients were randomised to receive PEG IFN, boceprevir 800mg three times a day, and RBV 400-1000mg. This was compared to triple therapy with PEG IFN, boceprevir 800mg and RBV 800-1400mg.

In the SPRINT -1 study it was rationalised that the lead-in strategy with 4 weeks of PEG IFN + RBV would allow PEG IFN + RBV steady-state concentrations by week 4. The study included 100 treatment naïve patients in each of the two arms. Both arms included patients with the presence of cirrhosis (6-9% in each arm) and African Americans (14-17% in each arm). The study showed that with all treatment options, boceprevir improved SVR rates. For the 28-week treatment inclusive of 4-week lead-in SVR rates were 56% and 54%.

Boceprevir-based triple therapy for 44 weeks plus 4-week lead-in showed a SVR rate of 75%.

The study also found up to 53% SVR rate for African American patients with the addition of boceprevir compared to a SVR rate of 23% for the same ethnicity patients treated with PEG IFN + RBV (Conjeevaram et al., 2006; Muir & Bornstein, 2004).

In a phase 3 retreatment with HCV Serine Protease Inhibitor Boceprevir and Peg Intron/Rebetol 2 (RESPOND-2) study of boceprevir 403 patients, patients were randomly assigned to one of three groups (Bacon et al., 2011). For all three groups PEG IFN + RBV were administered for 4 weeks. Then group 1, which was the control group, received placebo plus PEG IFN + RBV for 44 weeks. Group 2 received boceprevir plus PEG IFN + RBV for 32 weeks and patients with a detectable HCV RNA level at week 8 received placebo plus PEG IFN + RBV for an additional 12 weeks. Group 3 received boceprevir plus PEG IFN + RBV for 44 weeks. The conclusion of the study was that the addition of boceprevir to PEG IFN + RBV resulted in significantly higher rates of SVR in previously treated patients with chronic HCV genotype 1 infection, as compared to PEG IFN + RBV alone. The rate of SVR was significantly higher in the two boceprevir groups (group 2, 59%; group 3, 66%) than in
the control group (22%, P<0.001). Anaemia was a significantly higher side effect in the two boceprevir groups than in the control treatment.

A further study by Poordad and colleagues (2011) reported that when administered for 24- or 44-weeks’ triple therapy with boceprevir was associated with improved SVR of between 67% and 68%. The side effects identified in that study included anaemia and dysgeusia (distortion of the sense of taste). The aforementioned study was a double-blind SPRINT-2 phase 3 study. In this study there were two untreated genotype 1 cohorts: non-black participants and black participants. Participants were randomly assigned to one of three groups. All three groups received PEG IFN + RBV for one month and were randomly assigned to one of three groups. The first group received a placebo and PEG IFN + RBV for 24 weeks, the second (response-guided) group received boceprevir and PEG IFN + RBV for 24 weeks after a 4-week lead-in period with PEG IFN + RBV. Those with a detectable HCV RNA level between 8 and 24 weeks received a placebo plus PEG IFN + RBV for an additional 20 weeks. The third group received boceprevir and PEG IFN + RBV for 44 weeks. At the end of 44 weeks the non-black ethnic cohort had a 40% SVR response in the placebo group, a 67% response in the response-guided group and a 68% response in the third group. In the black ethnic cohort there was a 23% response in the first group, a 42 % response in the second group and a 44% response in the third group.

A further study in 2011 reported that RBV dose can be reduced to as low as 600mg per day without compromising the treatment response to triple therapy (Sulkowski et al., 2011a). Furthermore, a 2014 study found that boceprevir and telaprevir increased SVR but had a higher rate of adverse effects and therefore lesser clinical tolerance study (Lim et al., 2014). In summary, one could thus conclude that a greater percentage of HCV patients would not complete triple therapy compared to PEG IFN + RBV therapy, and for the percentage of
patients who did complete triple therapy, the SVR would be higher than that for patients who completed PEG IFN + RBV.

2.4.1. PREDICTORS OF TREATMENT OUTCOME IN TRIPLE THERAPY BEFORE AND AFTER TREATMENT COMMENCEMENT

Triple therapy improves SVR rates in HCV genotype 1 patients in comparison to SVR rates in PEG IFN + RBV therapy. However, treatment failure is a significant problem with triple therapy. Kwo and colleagues (2010) found that a RVR achieved by the addition of boceprevir predicted SVR regardless of the treatment arm in their study. That same study found that achieving EVR (undetectable HCV RNA at week 12 of triple therapy) also predicted SVR. It also concluded that patients who cleared the virus between 4 and 12 weeks of boceprevir treatment (late responders) were more likely to achieve SVR in the lead-in arms of their study if the patients received 48 weeks of therapy. Kwo and colleagues (2010) suggested that response-guided rules may be appropriate for boceprevir. They suggested that patients clearing the virus early may only require 28 weeks of treatment and late responders would benefit with an extension of therapy.

A study by Jacobson and colleagues (2012) sought to develop rules for the cessation of treatment for patients destined to fail triple therapy. They analysed data from the SPRINT-2 and RESPOND-2 studies to determine whether protocol-specified stopping rules could be refined and standardised. In reviewing SPRINT-2 data if the 12-week rule for cut-off with HCV RNA cut-off of greater or equal to 100IU/ mL had been used then 65 of the 195 treatment failures would have had their treatment stopped without affecting the SVR among 475 successes. In reviewing the RESPOND-2 data it was found that five of six patients with week 12 HCV RNA levels between the lower limit of detection (9.3 IU/mL) and the lower level of quantification (25 IU/mL) and who continued treatment despite the protocol-stipulated futility rule, achieved SVR. One patient who had a HCV RNA level of 148 IU/mL
at week 12 continued therapy and had undetectable HCV RNA at week 16 and attained SVR. The Jacobson and colleagues (2012) study concluded that with patients being treated with the triple therapy, including boceprevir, the combination of two stopping rules maximised the early cessation of futile therapy and minimised premature treatment discontinuation. The two stopping rules were a HCV RNA level greater or equal to 100 IU/mL at week 12 and detectable HCV RNA at week 24.

A study by Pearlman and Ehleben (2014) concluded that protease inhibitor therapy could be unnecessary in HCV genotype 1, non-cirrhosis, treatment naïve patients with low viral load at base line and who achieve SVR after 4 weeks of PEG IFN + RBV treatment. After 4 weeks of lead-in therapy with PEG IFN + RBV, 101 patients who represented 48% of the baseline patients had a RVR and were eligible to participate in the study. Patients were randomised equally to either 20 weeks of additional PEG IFN + RBV therapy or to 24 weeks of PEG IFN + RBV and boceprevir (triple therapy). The study found that there were no significant differences in rates of SVR-12 in patients treated with PEG IFN + RBV versus triple therapy. The researchers added that viral subtype (HCV genotype 1a or 1b), interleukin (IL) -28b genotype (CC or non-CC), and ethnicity (African-American versus non-Hispanic white) were not significant variables. In reference to the findings of the study, Wang and colleagues (2014) commented that similar patients with an unfavourable host genotype are less likely to respond to the PEG IFN + RBV therapy. In summary, the main pre-treatment predictors of treatment outcome are low baseline viral load and no, or mild, liver damage. The main predictors of treatment outcome once treatment has commenced are undetectable HCA RNA at week 4 of treatment (RVR) and undetectability of HCA RNA, or a greater than 2 log reduction in HCA RNA from baseline, in the first 12 weeks of treatment. Treatment failure is a significant problem with triple therapy (Bacon et al., 2011; Poordad et al., 2011).
2.4.2. TRIPLE THERAPY TREATMENT OF TREATMENT-NAÏVE PATIENTS

For treatment naïve patients triple therapy treatment might be stopped at week 28 if there is a very good virological response. In clinical trials, approximately two thirds of patients who were treatment-naïve cleared the virus when the treatment included a four-week lead-in with PEG IFN + RBV and 44 weeks of triple therapy (Poordad et al., 2011).

The SPRINT-2 phase 3 study (Poordad et al., 2011) investigated treatment-naïve patients after a four-week lead-in phase with PEG IFN + RBV. Patients were then randomised into 3 groups. The first group received PEG IFN + RBV for 44 weeks. The second group received PEG IFN + RBV and boceprevir from weeks 4 to 28. Patients in this group who had detectable virus from between 8 to 24 weeks were given a course of PEG IFN + RBV for an additional 20 weeks. Also, in this group those patients who showed undetectable virus between 8 weeks and 24 weeks stopped treatment at week 28. The third group receive boceprevir and PEG IFN + RBV for 44 weeks (total treatment period 48 weeks). The study found that the addition of boceprevir proved to be more effective than PEG IFN + RBV. SVR rates for the treatment with boceprevir ranged from 63% to 66% compared to 40% without boceprevir. In non-African American patients SVR rates for group 2 were similar to SVR results in group 3. This allowed for a shortened course of therapy in 44% of all treated patients in this study. In all three groups negative HCV RNA at the eighth week of treatment was highly predictive of SVR. Patients with cirrhosis were also investigated in this study and it was found that SVR was not different between the boceprevir and control groups. However, the sample size in this group of patients was small.

In summary, the addition of boceprevir to PEG IFN + RBV has been shown to be more effective than treatment with PEG IFN + RBV. In addition, the percentage of patients achieving SVR improves if treatment is extended from 28 weeks to 44 weeks.
2.4.3. **TRIPLE THERAPY FOR TREATMENT-EXPERIENCED PATIENTS**

For treatment-experienced patients triple therapy treatment might be stopped at week 36 if there is a very good virological response. Triple therapy is not as successful with treatment-experienced patients compared to treatment-naïve patients when it comes to SVR rates. The American Association for the Study of Liver Disease (AASLD) guidelines recommend re-treating partial responders, those whose viral loads dropped while on PEG IFN + RBV but were still detectable at the end of the study (Kwo et al., 2010).

The phase 3 trial (RESPOND-2) (Bacon et al., 2011) evaluated the efficacy of boceprevir in treatment-experienced patients. The study excluded previous null responders and the majority of patients were previous relapsers. In this study patients were randomised to receive PEG IFN + RBV or triple therapy. It was found that with all previously treated patients a SVR rate of only 21% was achieved in the PEG IFN + RBV only arm. Patients who had previously relapsed achieved greater response rates in all groups (69%-75%) when compared to previous non-responders (40% -52%). The factors that were associated with achieving SVR were being assigned to the boceprevir group, previous relapse compared to non-responders, low viral load at beginning of treatment, the absence of cirrhosis and > Log 10 IU/ mL decrease in HCV RNA at week 4. In summary, patients who had previously relapsed achieved a greater response rate than those who were previous non-responders.

2.4.4 **SIDE EFFECTS AND LIMITATIONS OF TRIPLE THERAPY**

Anaemia is a common side effect of treatment which includes boceprevir (Barritt & Fried, 2012). Furthermore, anaemia, which is also common adverse effect resulting from ribavirin, can be exacerbated by the addition of boceprevir. Boceprevir can affect the bone marrow and cause low red and white blood cell counts. If blood cell counts fall dangerously low then the result may be anaemia. It has been suggested that anaemia may represent a surrogate marker of ribavirin exposure in patients with genotype 1 (Sulkowski et al., 2011a).
Erythropoietin was used to manage anaemia in the SPRINT-1 study, in which the development of anaemia and erythropoietin use were associated with improved SVR (Kwo et al., 2010).

Adverse side effects reported of treatment-naïve participants in the SPRINT-1 study (Kwo et al., 2010) who received boceprevir triple therapy were (% of participants with side effects): fatigue (58%), anaemia (50%), nausea (46%), headaches (42%), dysgeusia (35%), insomnia (34%), chills (34%), alopecia (27%), neutropenia (25%), diarrhoea (25%), decreased appetite (25%), vomiting (20%), dizziness (19%), arthralgia (19%), dry skin (18%), asthenia (15%), irritability (11%), rash (17%) and dry mouth (11%). In addition to these side effects a 2011 study reported headaches as a side effect in 42% of participants treated with boceprevir triple therapy (Poordad et al., 2011). Boceprevir may also cause birth defects or death of an unborn baby. Therefore boceprevir is not to be taken if the patient is pregnant or their sexual partner is pregnant or plans to become pregnant (U.S. Food & Drug Administration, 2011b).

Further limitations include drug-drug interactions which restrict use of triple therapy and the high pill burden and complexity of treatment, both of which mean compliance is difficult and thus there is the potential of a lower response rate (Casey & Lee, 2013). There is a total of 459 drugs (2184 brand and generic names) which are known to interact with boceprevir of which 208 are major drug interactions (1188 brand and generic names). The optimal use of boceprevir requires a significant understanding of their clinical pharmacology and drug interaction potential (Kiser, Burton, Anderson, & Everson, 2012). Similar to PEG IFN + RBV treatment, few people can tolerate triple treatment (Gane et al., 2014) and also may be a reason for a reluctance to take up treatment. Finally, the triple therapy with boceprevir is only approved for the treatment of HCV genotype 1 patients (U.S. Food & Drug Administration, 2011a).
2.5 CRITERIA FOR HCV TREATMENT IN NZ

Patients are referred to the hospital’s Liver Unit by an infectious disease specialist, a gastroenterologist or the patient’s GP and if deemed to be a good candidate for treatment is then referred to the hospital’s HCV research nurses. The criteria for treatment may be different for each referring GP but the treating hospitals expect the patient to be clean from the use of illegal drugs for at least 6 months and to be under the age of 70. Patients who are using marijuana or who prescribed methadone are accepted for treatment. The hospitals treating HCV-infected patients with PEG IFN + RBV who participated in this study also used the Pegasys’ Summary of Product Characteristics (SPC) criteria treatment exclusion due to contraindications (Roche, 2009b). Section 4.3 of the SPC lists the following under contraindications:

- Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years of old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease within last six month
- HIV-HCV patients with cirrhosis and a Child – Pugh ≥ 6.

2.5.1 PHARMAC FUNDING OF HCV TREATMENT IN NZ

On 9 March 2009 PHARMAC announced the approval of the funding of PEG IFN + RBV for chronic HCV patients, effective from 1 April 2009 with specified treatment criteria (PHARMAC, 2009, p.2) (see Appendix C). PHARMAC announced on 9 August 2013 the
approval of the funding of triple therapy from 1 September 2013 (PHARMAC, 2013) (see Table 2.3). The PHARMAC notification listed specific restrictions on the availability of funded triple therapy (PHARMAC, 2013, p.2) (see Appendix D). The key dates in the PHARMAC funding of HCV treatments are set out in Appendix E. The prices of treatments negotiated by PHARMAC are detailed in Appendix F. On 10 August 2015 PHARMAC issued “A Request for Information - second generation DAA therapies “ (PHARMAC, 2015) (see Appendix G). The total drug costs for each PEG IFN + RBV and triple therapies treatment, based on the cost to PHARMAC, are listed in Appendix G.

2.6 SECOND GENERATION DIRECT ACTING ANTIVIRALS (DAAs)

The first generation DAAs, boceprevir-base and telaprevir-based triple therapies, increase the cure and sustained SVR rate compared to earlier therapies and may reduce the duration of treatment. However, because of the need for IFN and RBV and the significant adverse side effects, in particular anaemia and rashes, there is less clinical tolerance. Furthermore, triple therapy with either boceprevir or telaprevir requires extra care to avoid drug interactions. In addition, boceprevir and telaprevir are only licenced to treat HCV genotype 1 HCV patients (Lim et al., 2014). Because of these limitations it was recognised there was a need to develop newer classes of antiviral agents without the need for IFN, with or without RBV, and which would offer better response rates with shorter treatment periods. In recent years there have been encouraging developments of second generation DAAs. A list of current first and second generation DAAs is summarised in Appendix H. The HCV treatment drugs which have been approved by the FDA at the time of writing are listed in Appendix I.
2.7 FDA APPROVED SECOND GENERATION DAAs INTERFERON-FREE STUDY GROUP TRIALS

2.7.1 SOFOSBUVIR (SOLVADI)

On 6 December, 2013 FDA approved sofosbuvir for HCV for:

- HCV Genotypes 1 and 4 with PEG IFN + RBV 12-week treatment
- HCV genotype 2 with IFN-free plus RBV 12-week treatment
- HCV Genotype 3 with IFN-free plus RBV 24-week treatment

Three phase III trials which investigated sofosbuvir without interferon were the FISSION (Lawitz et al., 2013), POSITRON (Jacobson et al., 2013) and the FUSION (Jacobson et al., 2013) trials. Sofosbuvir was well tolerated in all three trials. The FISSION trial compared PEG IFN + RBV for 24 weeks of treatment with sofosbuvir plus RBV for 12 weeks of treatment in HCV genotypes 2 and 3 treatment-naïve patients. Both arms the 12 week and 24-week arms achieved similar SVR12 rates of 67%. However, SVR 12 rates for HCV genotype 2 patients 12-week treatment was 97% compared to the 24-week arm SVR24 rate of 78%. The SVR12 rate for genotype 3 patients 12-week treatment was 56% compared to the 24-week arm SVR24 rate of 63%. The POSITRON trials evaluated sofosbuvir plus RBV in 278 genotype 2 and 3 patients (53% and 47% respectively) for 12 weeks and who were intolerant, ineligible or unwilling for IFN-based therapy. The overall SVR12 rate was 78% (HCV genotype 2 SVR rate was 93% and HCV genotype 3 SVR12 rate was 61%). Finally, the FUSION trials evaluated the all-oral study group of sofosbuvir in 201 treatment-experienced HCV genotype 2 and 3 patients for 12 and 16 weeks. Overall SVR rates were 50% and 73% respectively. HCV genotype 2 SVR12 rate was 86% and SVR16 rate was 94%. The HCV genotype 3 SVR12 rate was 30% and SVR16 rate was 62%.
2.7.2  **SOFOSBUVIR/LEDIPASVIR (HARVONI)**

Sofosbuvir and ledipasvir therapy was approved by the FDA for the treatment of HCV genotype 1 treatment-naïve patients based on two registration trials: ION-1. (865 treatment-naïve patients; those with cirrhosis included), ION-3 (647 treatment-naïve patients; those with cirrhosis excluded). ION-1 investigated treatment duration (12 or 24 weeks) and the need for RBV. SVR 12 was 97% to 99% across all arms and there was no difference in SVR based on treatment duration, use of RBV or HCV genotype 1 subtype (Afdhal et al., 2014). The ION-3 investigated shortening therapy from 12 to 8 weeks (with or without ribavirin). SVR12 was 93% to 95% across all arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8 week treatment (20 of 431) regardless of RBV use when compared to 12 week treatment (3 of 216) (Kowdley et al., 2014).

2.7.3  **PARITAPREVIR/RITONAVIR/OMBITASVIR/DASABUVIR (PrOD (VIEKIRA PAK))**

Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) was approved by the FDA based on three registration trials: PEARL-IV, TURQUOISE-11, and SAPPHIRE-1. The PEARL-IV trial (305 treatment-naïve patients with genotype 1α without cirrhosis) was designed to determine the role of PrOD with or without weight-based RBV. SVR12 was lower in the RBV-free arm (90%) than in the RBV-containing arm (97%) owing to higher rates of virologic failure (7.8% versus 2% respectively) (Ferenci et al., 2014). The TURQUOISE-11 trial (261 treatment-naïve and experienced patients with HCV genotype 1a and cirrhosis) by Poordad and colleagues (2014) compared 12- and 24-week treatments with PrOD and RBV. SVR12 was 89% and SVR24 was 95%, the difference being primarily from patients with null response to PEG IFN + RBV. The difference in SVR rates in patients with cirrhosis who were naïve to therapy was 92% and 95% respectively. The SAPPHIRE-1 trial (322 treat-
naïve patients with genotype 1a HCV infection without cirrhosis) by Feld and colleagues (2014) reported a SVR12 of 95.3%. Virologic failure was higher for HCV patients with HCV genotype 1a (7 of 8 failures had genotype 1 a) than patients with HCV genotype 1b (1 virologic failure).

2.7.4 **SOFOSUBVIR/SIMEPREVIR (SOVALDI/OLYSIO)**

The FDA’s approval of Sofosbuvir/Simeprevir was based on data from the phase II COSMOS trial, a four-armed phase II study in which patients received the combination with or without RBV for 12 or 24 weeks (Lawitz et al., 2014). Patients were either treatment-naïve or had failed to respond to prior therapy. The trial showed that treatment duration and RBV had no effect on SVR12. In the 24-week arms, 93% of the 30 patients treated with RBV compared to 100% of the 16 who received RBV-free treatment. In the 12-week arms, 93% of the 27 patients treated with RBV which was the same for the SVR12 rate for the14 patients who received RBV-free treatment.

2.7.5 **SOFOSUBVIR/DACLATASVIR (SOLVADI/DAKLINZA)**

The phase III ALLY-2 trial for 12 weeks was the basis for the recommendation of the sofosbuvir and daclatasvir combination therapy for HCV genotypes 1, 2, 3 and 4 (Wyles et al., 2015). The trial assessed the efficacy and safety of the combination therapy for 12 weeks in patients co-infected with HCV (genotypes 1, 2, 3, and 4) and HIV. One hundred and twenty three (83%) of the patients were HCV genotype 1 and eighty three (54%) were treatment naïve. The SVR12 was 96% for HCV patients with HCV genotype

2.7.6 **PARITAPREVIR/RITONAVIR/OMBITASVIR (TECHNIVIE)**

Hezode and colleagues (2015) examined the efficacy and safety of an all-oral-IFN-free study group of ombitasvir, paritaprevir and ritonavir, with or without RBV in a study of 135 HCV genotype 4 HCV patients (PEARL-I). In treatment-naïve patients SVR12 rates for RBV and RBV-free were 100% and 90.9% respectively and in treatment-experienced patients
SVR12 rates of 100% were achieved for both RBV and RBV-free study groups. The PEARL-I study showed that the study group was well tolerated, with low rates of anaemia and low rates of discontinuation.

2.8 THE EUROPEAN ASSOCIATION for the STUDY of the LIVER (EASL) GUIDELINES

At the 50th International Liver Congress in April 2015 EASL released its latest HCV treatment guidelines which recommends any one of six new IFN-free treatments (see Appendix J). The Guidelines state that PEG IFN + RBV or triple therapy with either boceprevir or telaprevir remains acceptable only when none of the new options are available. If the new options or triple therapy with boceprevir or telaprevir are not available, then EASL recommends PEG IFN alfa-2a plus sofosbuvir + RBV for all genotypes and PEG IFN alfa-2a plus simeprevir + RBV for HCV genotypes 1 and 4 (see Appendix J). Standard duration of IFN-free therapy is 12 weeks. Persons with HCV genotype 1 and without cirrhosis are able to take sofosbuvir/ledipasvir for 8 weeks without ribavirin. The Guidelines state there is still a role for ribavirin and persons with genotype 1 and cirrhosis should include ribavirin or extend treatment for 24 weeks. Liver transplant recipients should include ribavirin in their interferon-free regime, but if that is not possible then treatment duration should be also extended. For decompensated cirrhosis the recommendation is sofosbuvir plus ribavirin (genotype 2 and 3), and sofosbuvir with either ledipasvir (genotypes 1, 4, 5, and 6) or daclatasvir (all genotypes).

2.9 FUTURE OF RIBAVIRIN THERAPY FOR HCV

Ribavirin remains an essential part of approved DAAs despite the lack of understanding of the mechanism of action of ribavirin and despite the reported toxicities and side effects such as anaemia (Koh & Liang, 2014). Because of the potential development of
highly effective DAA combinations regimes which have good tolerability and are easily administered the future role of ribavirin in the treatment of HCV is the subject of discussion.

The PEG IFN + RBV combination of drugs has been shown to be more clinically effective than either drug alone and therefore until recently this treatment study group has been the standard of therapy for the treatment of HCV (Brillanti et al., 1994; Ghany et al., 2009; Strader et al., 2004). A weight-based daily dosage of 1000 mg/d is recommended for genotype 1 patients weighing less than 75 kg. For patients weighing over 75kg a 1200 mg/d dosage is recommended. For genotype 2 and 3 patients a fixed dosage of 800 mg/d is recommended (Ghany et al., 2009; Strader et al., 2004). Studies have shown that higher doses of ribavirin (1400-3600 mg daily) have improved SVR in patients but the side effects were reported to be unacceptable (Jacobson, Brown, & McCone, 2007; Lindahl, Stahle, Bruchfeld, & Schvarcz, 2005).

The use of RBV produces numerous physiological and psychological side effects (Mayo Clinic, 2016b). These side effects of RBV, even with recommended dosage, have meant that some patients have not been able to complete their therapy (Bodenheimer et al., 1997). Previous studies have found that ribavirin was associated with depression when used as a monotherapy for treatment of HCV (Bodenheimer et al., 1997).

The first DAAs triple therapy approved by the FDA for patients with HCV genotype 1 included RBV (Bacon et al., 2011; Hezode, Forestier, & Dusheiko, 2009; Jacobson et al., 2011; Poordad et al., 2011). Whilst triple therapy significantly improved SVR rates there is poor tolerability due to the additional side effects (Poordad et al., 2011). In studies of triple therapy it was reported that RBV dosage could be reduced to as low as 600mg per day without affecting the treatment response (Sulkowski et al., 2011a; Sulkowski, Reddy, & Afdhal, 2011b). The implications of the findings of these two studies are that in combination with DAAs the maximal dosage of RBV may not be required. Studies have also shown that in
the treatment of HCV genotypes 2 and 3 patients, single DAA (sofosbuvir) and RBV therapy for 16 weeks is no less effective that PEG IFN +RBV therapy (Gane et al., 2013; Jacobson et al., 2013; Lawitz & Gane, 2012; Osinusi, Meissner, & Lee, 2013; Zeuzem, Dusheiko, & Salupere, 2013). The Gane and colleagues (2013) study also found that 60% of HCV genotypes 2 and 3 patients achieved a SVR with sofosbuvir monotherapy, but 100% of patients achieved SVR when treated with sofosbuvir and RBV. This result indicated the importance of RBV in the treatment of patients with HCV genotypes 2 and 3.

There are a number of past and current studies investigating RBV-free study groups. An early clinical trial by Gane and colleagues (2010) showed antiviral activity in an all-oral DAA combination without RBV. Subsequently there have been a number of studies with RBV-free DAA study groups. A 2012 study with 18 treatment naïve HCV genotype 1b patients treated for 24 weeks with the two DAAs asunaprevir and daclatasvir showed a SVR12 of 83% (Lok, Gardiner, & Hezode, 2012). Another study with the same treatment study group reported a 64% SVR for treatment naïve HCV genotype 1b patients and a 90% SVR null responder experience HCV genotype 1b patients (Suzuki, Ikeda, & Suzuki, 2013). A 24 week study by Sulkowski and colleagues (2013) using the two DAAs sofosbuvir and daclatasvir reported a SVR of 100% for treatment naïve HCV genotype 1b patients, a SVR from 88%-100% for treatment-naïve HCV genotypes 2 and 3 patients and a SVR of 100% for HCV genotype 1 previous non-responders.

Lawitz and colleagues (2013b) conducted two studies using two DAAs without RBV. The C-WORTHY 2013 study with treatment-naïve HCV genotype 1 patients used the DAAs MK-5172(PI) plus 50mg MK-8742 (NS5A) showed a SVR12 of 100%. The LONESTAR study (Lawitz et al., 2013a) with sofosbuvir and ledipasvir showed a SVR12 of 95% for both treatment naïve HCV genotype 1 patients for a 8 week and 12 week treatment. In the same study HCV genotype 1 patients who had previously failed showed a SVR12 of 100%.
An Everson and colleagues (2013a) 24-week study using the same treatment study group plus a third DAA, BMS-791325, with treatment-naïve HCV genotype 1 patients, showed a SVR4 of 94% and a SVR12 ranging from 89% to 92%. A further study result with the same study group for a 12 week treatment period with HCV genotype 1 treatment naïve patients showed a SVR of 94% (Everson, Sims, & Thuluvath, 2013b). The AVIATOR study with HCV genotype 1 treatment naïve patients also using three DAAs without the use of showed a SVR of 87% (Kowdley & Poordad, 2013). These studies show that successful treatment of HCV is possible with combination therapy using DAAs without RBV particularly in patients with HCV genotype 1. RBV may continue to be part of a combination therapy but with the development of more potent DAAs to attack multiple HCV targets the use of RBV may not be necessary. The decision on the type of therapy and the decision to continue with a treatment which includes RBV may, in many cases, be influenced by the cost of the therapy especially in developing countries. A course of therapy with RBV ranges from US$4,500 for HCV genotypes 2 and 3 to US$13,500 for HCV genotype 1 (48 weeks and <75kg patient weight). The current cost of a treatment course of a FDA approved single DAA range from US$26,000 to US$49,000 (excluding PEG IFN + RBV). PHARMAC funding costs for PEG IFN + RBV and triple therapy are listed in Appendices F and G.

2.10 COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) IN THE TREATMENT OF HCV

Homeopathy is a non-toxic medical system which uses highly diluted pathogens or potentially toxic substances as remedies (Cutler, 2011). Homeopathic treatment uses natural substances that are derived from plants, minerals and animals (National Centre for Complementary and Integrative Health, 2016). Some of the homeopathic remedies that might be used are: aconite, arnica, arsenic, belladonna, carduus marianus, chelidonium, cornus circinata, ferrum metalliicum, glycyrrhizin, lycopodium, mercurius, myrica cerifera, nux
vomica and china officinaills and thuja (British Homeopathic Association, 2016; Cutler, 2011; National Centre for Complementary and Integrative Health, 2016). In homeopathy there are particular medicines for particular sets of symptoms but there is no fixed medicine for any particular illness or disease (National Centre for Homeopathy, 2016). This makes it difficult to carry out clinical trials given the lack of randomised controlled trials (Feinstein, 1980).

Cutler (2011) stated that for patients who cannot be treated with antiviral drugs the use of homeopathy or medicinal herbs may be an option. However, Cutler (2011) did not provide the results of studies or research to support this claim. Cutler (2011) also stated that homeopathic treatment of HCV is more likely to be practiced in Europe than in the United States. Furthermore, in Asia there has been a lower acceptance of antiviral therapy compared to the use of medicinal herbs (Nishioka, 2007). Some examples of the percentage adoption of antiviral prescriptions for the treatment of HCV are: Japan (10%), China (20-30%), Korea (1%) and Indonesia (3-5%). On the other hand, the herbal preparation glycyrrhizin which is based on an extract of liquorice is used in the treatment of 30% of HCV-infected patients in Japan, 20-30% of patients in China and 3-5% of patients in Indonesia. Other medicinal herbs used in Asian countries are ursodeoxycholic acid (UDCA) and Sho-saiko-to (Nishioka, 2007).

One study reported the long term administration of glycyrrhizin in the treatment of Chaos effective in preventing HCC (Arase, Ikeda, & Murashima, 1997). It has also been reported that while an ALT response induced by four weeks of glycyrrhizin therapy can be maintained in a subset of CHC patients receiving at least 3 injections weekly, the ALT response did not translate into significant histological improvement after six months of treatment. In that study the relative risk of HCC incidence in patients treated with
glycyrrhizin was 2.49 times more compared to patients treated with glycyrrhizin (Orlent et al., 2006).

Contrary to Cutler (2011) a meta-analysis of every trial of complementary and alternative medicines published in English between 1966 and 2002 concluded the use of herbal supplements for the routine treatment of any chronic liver disease could not be recommended (Levy, Seeff, & Lindor, 2004). Furthermore, Kudha-Bukhsh (2003, p.339) stated that:

“while clinical effects of some homeopathic drugs could be convincingly shown, one of the greatest objections to this science lies in its inability to explain the mechanism of action of the micro doses based on scientific experimentations and proofs”.

Kudha-Bukhsh (2003) concluded that well thought out research studies will yield an understanding of the molecular mechanisms of ultra-low doses of homeopathic drugs.

Rambaldi and colleagues (2007) reported on their study of carduus marianus (milk thistle) stating their results questioned the beneficial effects of milk thistle for patients with alcoholic and/or HBV or HCV. They also reported their results highlighted the lack of high-quality evidence to support milk thistle homeopathic intervention and adequately conducted and reported randomised clinical trials on milk thistle versus placebo are needed. A systematic review of in vitro research with high homeopathic potencies found that those reviewed experiments were not homogeneous in design or quality (Witt et al., 2007). Witt and colleagues (2007) concluded that in order to establish models that are stable across laboratories and teams, more independent replications should be done. The review also concluded that blinding and randomisation would strengthen the evidence of future experiments. Finally, there are no high-quality scientific studies to show that homeopathy is any more effective than a placebo (National Centre for Complementary and Integrative Health, 2016; Wanjek, 2013).
2.11 GENDER DIFFERENCES IN HCV TREATMENT

While there have been various studies which have investigated both PEG IFN + RBV and triple therapy, there have been few studies which have investigated gender differences during those therapies. One study which investigated therapy with IFN compared patients who showed elimination of HCV RNA for 6 months after the termination of treatment. The rate of complete response was 33% in males aged 39 years or less, 25% in males aged 40 years or older, 75% in females younger than 39 years of age and 15.6% in females aged 40 years and older (Hayashi et al., 1998). That study suggested that hormonal activity, in particular the level of estrogen, may be associated with the sustained elimination of HCV. A more recent study by Sezaki and colleagues (2009) reported the response to PEG IFN + RBV was poorer in female patients ≥ 50 years compared to male patients ≥ 50 years, irrespective of compliance with treatment. It was also suggested that lower estrogen levels in women ≥ 50 years, could be responsible for their impaired response to PEG-IFN + RBV (Sezaki et al., 2009).

Another study which investigated 181 genotype 1 chronic HCV patients being treated with PEG IFN + RBV between 2001 and 2007 found no gender difference in SVR (Narcisco-Schiavon et al., 2010). In that study the mean age was 46.4 (SD = 11.0) and 46% were females. When compared to males, females had higher instances of adverse effects such as higher need for dose reduction, for both PEG-IFN (p = 0.004) and RBV (p = 0.006) and a higher incidence of anaemia (p < .001), dizziness (p = 0.011), decreased visual acuity (p = 0.025), alopecia (p = 0.011), nausea (p = 0.005), anorexia (p < 0.001), bacterial infection (p = 0.025), and hypothyroidism (p = 0.036). However SVR did not differ between males and females (41% and 45% respectively, p = 0.464) (Narciso-Schiavon et al., 2010). Finally, anaemia is a serious and common side effect of RBV and because women lose blood each month through menstruation, they are more likely to develop anaemia (Cutler, 2014).
2.12 SUMMARY

The cost of the HCV in both economic terms and QOL is significant. HCV is a preventable but despite the knowledge of transmission and the literature available, HCV still remains a major health problem in New Zealand and world-wide. Diagnosis is difficult due to the fact that HCV is a highly asymptomatic illness and because the severity of patient’s symptoms are not linked with clinical or biological markers of disease progression. However, because of problems with diagnoses, HCV may go undetected for some time thus treatment may be delayed. Furthermore, studies have reported persons with a low viral load have better treatment outcomes compared to persons with a high viral load.

Therefore, the early screening for HCV for those persons identified as at-risk to HCV is critical. There is no vaccine for HCV therefore the elimination at present is reliant on an effective treatment. Until recently the treatment of choice for HCV was PEG IFN + RBV. This treatment is effective for approximately 75-80% of genotype 2 and 3 cases achieving SVR and approximately 40-55% in genotype 1 and 4 cases achieving SVR. However, the treatment is demanding on patients and the side effects can be severe. One of the most significant side effects to PEG IFN + RBV and triple therapies is depression, which may affect adherence to treatment. Certain clinical variables such as genotype and viral load are predictive of treatment success measured as SVR. However, the most compelling prediction of SVR is EVR.

First generation protease inhibitors boceprevir and telaprevir in combination with PEG IFN+ RBV (triple therapy) have shown improved SVR rates when compared to PEG IFN + RBV treatment. However, boceprevir-based and telaprevir-based triple therapies have tolerability issues because of the need for PEG-IFN +RBV. Furthermore; there are added side effects of protease inhibitors such as anaemia and rashes. Also, triple therapy is approved only for HCV genotype 1.
Because of the high level of intolerance and adverse side effects with IFN and RBV, new IFN-free drug therapies with or without RBV have been developed or are in the process of being developed. Combining different DAAs which target different steps of HCV replication should remove the need for IFN and possibly RBV and thus increase the tolerability of therapy. At the time of writing the FDA had approved the IFN-free DAAs; Harvoni, Olysio, Viekira Pak, Dakliza and Technivie. Besides the need for an IFN-free therapy there is also a medical need for an all oral, shorter duration therapy for HCV which is effective across all genotypes and also includes patients with cirrhosis and who have previously been non-responsive to PEG IFN + RBV therapy or triple therapy.

At the time of writing PHARMAC in New Zealand was funding both the PEG IFN + RBV therapy and triple therapy and recently on October 1st 2016, Vielera Pak.

While there have been few studies on the gender influence on treatment, some studies have shown differences in SVR between genders, while other studies have shown no difference in SVR, but differences in adverse effects such as anaemia and a higher need for dose reduction.

Studies have shown illness related dysfunction during treatment and post treatment is not often explained by physiological measures of disease severity and that psychological factors may be associated with the effectiveness of treatment outcome and treatment adherence. In addition, successful treatment of HCV should not only be measured in terms of SVR, but should also include the measurement of improvement in the patient’s QOL and the factors that contribute to a patient’s QOL.

The following chapter will discuss how psychological symptoms may have a relationship with treatment outcomes and also how the understanding of those symptoms may be used to better understand and predict treatment success and patient treatment adherence. Significant findings may mean that interventions can be designed to improve the success of
PEG IFN + RBV therapy and triple therapy. Successful interventions can be measured by the assessing changes to QOL, fatigue, sleep disorders, mood states, depression, anxiety, cognitive dysfunction and patient treatment satisfaction during treatment and post treatment.

Non-responders are patients who have detectable serum HCV RNA at the end of the treatment for HCV infection (Farnik et al., 2009). For the present study it is the detectable serum HCV RNA at the end of PEG IFN + RBV therapy and triple therapy. The clinical variables that tend to produce a non-response to the treatment are infection with HCV genotype 1 and a high pre-treatment viral load. Host related factors such as liver fibrosis and ethnicity also affect response (Mihm, Herrmann, Sarrazin, & Zeuzem, 2006). The Mihm and colleagues (2006) study reported that the reasons host factors and ethnicity are related to a non-response to treatment was not evident.
CHAPTER THREE
PSYCHOLOGICAL SYMPTOMS AND HCV, PEG IFN + RBV THERAPY AND TRIPLE THERAPY

3.0 INTRODUCTION

While PEG IFN + RBV therapy and triple therapy are still in use it is relevant to research psychological symptoms and clinical outcomes to assess and quantify the impact of those therapies. From the literature and anecdotally from discussions with research nurses at Auckland and Greenlane Gastroenterology Clinics, there is evidence that persons with HCV may have impaired psychological symptoms. Furthermore, treatment with PEG IFN, with or without RBV, and first generation DAAs, such as boceprevir-based triple therapy (boceprevir plus PEG IFN + RBV) have been shown to exacerbate psychological symptoms. Studies have also reported that these problems may persist for many months after the cessation of treatment (Hopwood, 2009). One United Kingdom web-based survey of 500 patients, who had completed the PEG IFN + RBV therapy, reported that 90% of patients continued to experience ongoing symptoms or side effects for longer than 12 months after treatment end. Furthermore, of those who had attained SVR, 36 % reported feeling “worse” after treatment than before treatment (The Hepatitis C Trust, 2007). New second generation DAA drugs which are continuing to be developed require shorter treatment times, have less side effects and higher efficacy rates, than PEG IFN + RBV and triple therapy (Younossi & Henry, 2015; Younossi, Stepanova, Nader, Lam, & Hunt, 2015a).

There have been a number of quantitative and qualitative studies which have investigated the effect of PEG IFN + RBV on the psychological symptoms of depression and HRQL. However, there is a paucity of studies which have investigated other psychological factors affected by PEG IFN + RBV therapy which may have an effect on treatment
adherence and outcomes. In addition, there have been limited studies which have investigated the effect of triple therapy on psychological symptoms. Research involving New Zealand patients with HCV infection and PEG IFN + RBV and triple therapies is even more limited.

Research has shown that psychological effects such as QOL and HRQL, fatigue and sleep disorders, mood state disturbance, depression, anxiety, cognitive dysfunctions and patient dissatisfaction may affect persons with HCV infection. These effects may also play a role in treatment adherence and treatment outcome for both the PEG IFN + RBV and triple therapies. Therefore, research will be investigated by critically reviewing the literature relating to these effects in association with HCV-infected patients and PEG IFN + RBV and triple therapies at treatment end and three-month follow-up to treatment end.

3.1 HEALTH PSYCHOLOGY AND HCV

The World Health Organization (WHO) recognised that a person’s health was not limited to physiological wellbeing. In 1948 the WHO defined health as ‘a complete state of physical, mental, and social well-being and not merely the absence of disease or infirmity’ (World Health Organization, 1948). Division 38 (Health Psychology) of the American Psychological Association (APA) states that health psychology involves the scientific relations among psychological factors, behaviour and physical health and illness (American Psychological Association, 2016). It is the application of psychological theory, methods and research to health, physical illness and health care and is concerned with the psychological aspects of promotion, improvement and maintenance of health (Marks et al., 2003). Health psychology involves the study of a range of issues including QOL, HRQL, sleep, depression and anxiety (Uyemura, 2014). Health psychology also involves the psychological effect on how a person stays healthy, the reasons they become ill, and their responses when they become ill. Furthermore, it concentrates on health promotion and maintenance, prevention and treatment of illness. In considering the causes of illness, health psychology focuses in
particular on the behavioural and social factors that contribute to a person’s illness or dysfunction. Health psychology is also involved in the improvement of the health care system and the formulation of health policy (Taylor, 2008).

The experience of chronic illness causes psychological consequences and necessitates adjustment in multiple life domains across the course of the disease (Stanton, Revenson, & Tennen, 2007). The idea that psychological, social and physiological factors determine health and illness outcomes suggests a model for studying those issues. This model is called the biopsychosocial model (Taylor, 2008). This model is an extension of the biomedical model of health which attributes illnesses to biological determinants (Havelka, Lucanin, & Lucanin, 2009). The biopsychosocial model is a theoretical model that purports biological, psychological and social factors all play a significant role in illness and health and not biology alone (see Figure 3.1). Developing a model of the reasons why a patient may suffer from a disorder may assist health professionals in the diagnosis and treatment of patients.

Health psychology studies have shown that the strongest evidence that chronic illness increases life disruption is offered by large-scale, prospective studies (Michael, Kawachi, Berkman, Holmes, & Colditz, 2000; Polsky, Doshi, Marcus, Oslin, & Rothbard, 2005). Examples of the application of health psychology in practice are: Assessing QOL in patients with chronic illness (Hauser, Zimmer, Schiedermaier, & Grandr, 2004), non-pharmacological management of chronic pain (Turk, Burwinkle, Kenkel, & Brown, 2005; Turk & Okifuji, 2002), coping with chronic illness (Cheng, Hui, & Lam, 2004), the study and behavioural intervention for sleep dysfunction (Irwin, Cole, & Nicassio, 2006), the treatment of depression and fatigue, and the alleviation of psychological distress and improved functioning by reducing symptoms associated with an illness (Mohr, Hart, & Goldberg, 2003) and the assessment and treatment of anxiety in patients before therapy begins (Stauder &
HCV infection and treatment, while having physiological affects, also have important psychological affects and social outcomes. These affects or outcomes in many cases require significant psychological adjustments for individuals. Studies have shown that HCV infection is associated with lower QOL and HRQL, fatigue, sleep disorders, depressed mood states, depression and anxiety, and decreased cognitive function. The results of these studies suggest that the application of health psychology to patients with HCV infection is appropriate. Furthermore, the importance of health psychology in the context of HCV therapy is that

*Figure 3.1. Diagram of the biopsychosocial model,*
treatment success cannot just be measured in physiological terms but must also consider the psychological health and wellbeing of the patient.

3.2 QUALITY OF LIFE (QOL) AND HEALTH-RELATED QUALITY OF LIFE (HRQL), AND HCV

3.2.1 DEFINITION OF QUALITY OF LIFE (QOL) AND HEALTH-RELATED QUALITY OF LIFE (HRQL)

Quality of life (QOL) and health-related quality of life (HRQL) are often used interchangeably. However, there are differences in these two constructs. While there are differences, both QOL and HRQL measure subjective perceptions of a patient’s health and wellbeing.

Quality of Life (QOL)

The definition of QOL includes all aspects of an individual’s life. Studies have shown that acceptable standards of living alone do not correlate with subjective measures of life satisfaction (Pirfo et al., 1994). Frisch and colleagues (2005) stated that no variable is more clinically important or significant than QOL and that when treatment leads to improved QOL as well as to symptomatic improvement, then it can be said that significant change has been achieved. There have been a number of researchers who have contributed towards the understanding of what QOL encompasses. Felce and Perry (1995) commented that QOL includes a broad range of individual values and life domains and can be categorised within five dimensions: physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing and development and activity.

Patrick and Bergner (1990) stated that QOL is a multidimensional concept which encompasses the domains of an individual’s well-being; physical and cognitive capabilities,
functional behaviour, psychosocial adjustment, emotional status and economic well-being. It must include all areas of an individual’s life and experience.

QOL takes into account the impact of illness and treatment (Calman, 1984) and has been referred to as a broad and idiosyncratic construct which is only moderately affected by health (Feldman, Grundland, McCullough, & Wright, 2000). Younossi and colleagues (2007) stated that any assessment of QOL includes the effect of health on well-being and incorporates environmental and economic features of a person or group of patients.

QOL in many cases is associated with life satisfaction in psychology and psychiatry and to a lesser extent in general medicine (Cornell, Saunders, Paunovich, & Frisch, 1997; Trivedi et al., 2006). Life satisfaction has been defined as a “cognitive judgemental process dependent upon a comparison of one’s circumstances with what is thought to be an appropriate standard” (Diener, Emmons, Larsen, & Griffin, 1985, p.71).

While QOL in psychiatry is becoming more defined in terms of the psychological construct of life satisfaction, general medical and the pharmaceutical industry define QOL in terms of functional abilities or impairments as measured by the ‘Standard Form’ or the SF-12 or SF-36, and in doing so ignore the psychological aspects of QOL (Frisch et al., 2005). Frisch and colleagues (2005, p. 73) further stated that “in addition to a cure or management of symptoms, disease or disability, there is a desire to see a patients’ ability to function in everyday life enhanced or at least maintained after treatment”. However, these measures of functioning can miss signs of deep dissatisfaction or a very low QOL even though a person’s functioning is only mildly or moderately impaired (Frisch et al., 2005). A review of studies showed little relationship between objective (e.g. functional abilities or impairments) and subjective (e.g. attitudes and expectations) indicators (Diener & Seligman, 2004). It has been suggested that impairments in functioning that do not affect life satisfaction should not be considered in QOL assessment, and that life satisfaction replace measures of “functional...
ability “or supplements them. Furthermore, it has also been suggested that life satisfaction be considered a cognitive function in its own right and be included in measures such as SF-12 and SF-36 (Frisch et al., 2005).

_Health Related Quality of Life (HRQL)_

HRQL is more directly related to health in contrast to QOL (Martin, Sheridan & Younossi, 2002) and assesses how a patient’s well-being may be affected by a disease, disability or treatment (Bottomley, 2002). HRQL is important in managing patient health and treatment (Guyatt, Feeny, & Patrick, 1993) and is now more multidimensional than earlier versions of HRQL which concentrated on assessment of physical abilities. In contrast to earlier versions of HRQL, the current definition encompasses physical, social, emotional, cognitive, spiritual, and financial and work-related issues. Younosi and colleagues (2007) stated HRQL is less global than QOL and more directly related to health.

HRQL is commonly measured by the SF-36 questionnaire (Ware, Kosinski, & Keller, 1991). The SF-36 comprises 8 scales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health/Emotional Well-being (MH) which are weighted sums of the questions in their sections. The lower the score the more disability. The 8 scales are further summarised into the Physical Component Summary (PCS) which comprises the PF, RP, BP and GH scales, and the Mental Component Summary (MCS) which comprises the VT, SF, RE and MH scales.

In summary, while HRQL measures aspects of life related to health, QOL measures other aspects of life such as the life satisfaction, social environment, goals, values, work, self-esteem etc.
While HCV may progress to cirrhosis, there is still a significant impairment of QOL in many HCV patients prior to the onset of advanced liver disease (Foster, Goldin, & Thomas, 1998; Kenny-Walsh, 1999; von Wagner, Lee, & Kronenberger, 2006; Wiese et al., 2000). Strauss and colleagues (2014) found the presence of HCV in the early stages was associated with worse QOL. Interestingly in a study of injecting drug users, a worse QOL was reported by patients aware of their HCV-RNA status compared to those who were not aware of their infection. In addition, those who were not aware of their HCV infection had a worse QOL when compared to otherwise compatible non-HCV individuals. Researchers have suggested that the results indicated that HCV infection alone was associated with an impairment to the QOL of a patient and concluded that reduced QOL may have been partially an effect of labelling (Rodger, Jolley, Thompson, Lanigan, & Crofts, 1999).

It was been reported that patients with HCV have diminished HRQL as measured by SF-36 when compared with healthy controls and that the impact of HCV was most evident in the SF, PF, GH and VT scales of that measure (McHutchison et al., 2001). Furthermore, studies have indicated diminished HRQL in HCV-infected patients in neurological anchors (subclinical cognitive dysfunction) (Kramer et al., 2002), psychological anchors (including depression, psychiatric comorbidity and emotional distress) (Fontana et al., 2002; Fontana et al., 2001; Gallegos-Orozco et al., 2003; Hussain et al., 2001) and the social anchor “stigmatization” (Zichmund et al., 2003).

Tillman and colleagues (2011) reported on two independent prospective cross-sectional studies of 511 and 284 patients called the Hannover Study and the Leipzig Study respectively. The two studies looked at HRQL in patients with liver disease including HCV,
HBV, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH) and “other” liver diseases. In both studies patients with HCV scored worse in the mental health aspects of HRQL compared to other liver diseases except for HBV in one study.

The Hannover study investigated patients at the liver outpatient clinic at Hannover Medical School between 15th March 2001 and 15th October 2002 using the Health-related Quality of Life survey Short Form version 1 (Ware & Sherbourne, 1992) and the Fatigue Impact Scale (FIS) (Fisk et al., 1994). The study included a group of East Germans who had been infected with HCV contaminated anti-D immunoglobin and who had been followed by researchers since their infection in 1978/79. This study found there was no difference in the PCS for patients with HCV versus non-HCV patients. However, there was a significant difference in the MCS (p < 0.001). The study reported the major impairments were in the subscales VT (p < 0.05), SF (p < 0.004) and MH (p < 0.001). In addition, HCV showed the highest impairment in mental wellbeing compared to all but HBV at a level of significance (p < 0.05). The study showed in pair wise comparisons, that in MH aspects, the greatest impairment was seen in HCV patients. In addition, when analysing the different dimensions in the SF-36 results over the different liver diseases, patients with HCV were the most impaired in SF and MH scores.

The Leipzig study investigated a total of 284 patients who completed the SF-36, the World Health Organisation Quality of Life-BREF (WHOQOL-BREF)(The WHOQOL Group, 1998) and Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) questionnaires. The WHOQOL-BREF is a short, generic and transcultural assessment of the individual’s perceptions of their culture and value systems and their personal goals. The domains measured are physical health, psychological health, social relationships and environment. Most of the patients (N=157) suffered from HCV. Patients with HCV showed
significantly impaired HRQL compared to other patients with liver diseases in both the physical component scores: RP \((p < 0.02)\) and BP \((p < 0.05)\) and the mental component scores: VT \((p < 0.03)\), SF \((p < 0.01)\), RE \((p < 0.02)\) and MH \((p < 0.005)\) (Tillman et al., 2011).

Both the Hannover and Leipzig studies showed there was greater mental impairment in HCV patients compared to other liver diseases, although patients with primary biliary cirrhosis (PBC) showed a higher impairment in physical well-being. However, a similar study found that 18 patients with PBC were similarly impaired compared to 60 patients with HCV in both MCS and PCS (Bondini, Kallman, & Dan, 2007). An earlier study by Miller and colleagues (2001) reported that for untreated HCV-infected patients, mean SF-36 scores were significantly lower, across all modalities, than population norms. That study also reported SF-36 scores differed significantly according to age, gender, mode of infection, alcohol and methadone use, and satisfaction with social support. Miller and colleagues (2001) reported mean SF-36 scores did not differ significantly according to perceived or actual ALT level or pattern of ALT activity and concluded ALT levels were of limited usefulness in ascertaining a person’s sense of wellbeing and QOL in HCV-infection. Foster (2009) stated that in most chronic diseases physical impairment is more pronounced than mental impairment although there is support of the view that patients with HCV may be unexpectedly impaired in mental health compared to their impairment in physical functioning. A 2005 systematic review of HRQL studies found that patients with HCV scored lower than controls across all scales of the SF-36. The data showed that patients achieving SVR scored higher in all 8 of the SF-36 scales compared to patients without SVR and that this was particularly evident in the physical health domains. The data showed that the VT, GH, PF and SF scales in the SF-36 were the most relevant in patients with HCV (Spiegel et al., 2005).
Furthermore, chronic liver disease can reduce HRQL independently of type or severity of disease (Younossi et al., 2001). Researchers have shown that there is an association between chronic infection with HCV and a number of extrahepatic manifestations (EHMS) including neurological complications. Most EHMS, however, may improve or may be resolved after SVR (Monaco et al., 2012). The results of those studies which show little or no improvement in HRQL despite achieving SVR would tend to indicate that host-related rather than virus-related factors may reduce HRQL.

3.2.3 QOL AND HRQL AND THE RELATIONSHIP TO OTHER PSYCHOLOGICAL EFFECTS.

The prospect that the patient may be affected by hepatitis C for the remainder of their lives, concerns about symptoms and the disease itself may also lead to a lower quality of life (Strauss, 2006). Poor quality of life parameters for hepatitis C patients include: decreased general health perception, poorer mental health, and decreased physical function, social function, and vitality. Furthermore, Heerren and colleagues (2014) found that HRQL and fatigue scores correlated with sleep dysfunction and daytime sleepiness. Furthermore, Kallman and colleagues (2007) reported that for both HCV-infected and non-infected control groups chronic fatigue was related to a decrease in HRQL.

Multivariate analysis shows fatigue, insomnia and depression are important predictors of HCV patient’s HRQL prior, during, and after treatment, and that anaemia and receiving IFN were predictors of decreased HRQL during HCV treatment. Furthermore, anxiety have been found to be a major predictor of HRQL (Younossi et al., 2014a). There have been a few studies which have investigated the relationship between fatigue and QOL and HRQL. A subsequent study found that, in patients with chronic liver disease, fatigue was strongly related to HRQL (Gutteling et al., 2006). A further study by Hauser and colleagues (2004a) found that HRQL was affected by psychiatric and active comorbidities. Furthermore, it has
been reported that fatigue is an independent predictor of low HRQL (Kramer et al., 2005) and that fatigue is more closely associated with depression than with HCV (Barkhuizen et al., 1999; Gutteling et al., 2006; Poynard et al., 2002; Rodger et al., 1999).

3.2.4 QOL AND HRQL AND HCV TREATMENT

Studies have shown impairment in both HRQL and neuropsychological functioning during PEG IFN + RBV therapy (Dan et al., 2006). In addition, patients with IFN-induced SVR have shown greater, but not significant, impairment in both the PCS and MCS of the SF-36 compared to patients with CHC. Patients with interferon-based SVR scored worse on the SF-36 measure than those patients who were cleared spontaneously (Tillman et al., 2011).

A 2012 study investigated the impact on HRQL of boceprevir-based triple therapy and telaprevir-based triple therapy. At baseline 87 patients (68 telaprevir-based) completed the SF-36. At week 12 of treatment there was a drop in mean scores in all 8 of the SF-36 scales for both treatment groups. At week 24 of treatment analysis of the boceprevir-based triple therapy group (N=6) showed a significant worsening of the SF scale (Mousa, 2012).

A 2015 Brazilian study of 32 patients (17 treated with PEG IFN + RBV, 15 treated with telaprevir-based triple therapy) reported that patients treated with the triple therapy had a greater decrement in QOL indices. The study used the SF-36 and Chronic Liver Diseases Questionnaire (CLFQ) measures. According to the SF-36 measure the most significant decreases in the PCS, specifically in functional capacity. It was reported that week 12 was the most critical during treatment and at week 16 (4 weeks after withdrawal of telaprevir) there was a recovery of HRQL but still remained lower than patients on PEG IFN + RBV therapy (Fagundes et al., 2015).

Younossi and colleagues (2014a) recently reported on the impact of PEG IFN + RBV, sofosbuvir (SOF) + RBV, IFN + RBV, SOF + PEG IFN + RBV and a placebo in various
comparisons and durations. CHC patients were assessed using SF-36. Assessments were compared between treatment arms and also at baseline, during treatment, at the end of treatment, and at 4-week follow-up. The first analysis compared the summary scores and scales scores of SF-36 between SOF + RBV and placebo. When the two arms were compared directly no differences in MCS and PCS scores were observed at all time points. Only a decrement of 13.86 in the SF scale was found to be significantly more in the SOF and RBV arm when compared to the placebo arm ($p = 0.01$). After 4 weeks of follow-up, no significant decrements in any aspect of HRQL were observed between the 2 study arms (all $p < .10$).

The second analysis compared HRQL scores to their respective baseline scores. HRQL decrements were found in patients receiving SOF and RBV in both PCS ($p = 0.015$) and MCS ($p < 0.001$) scores, however there were no decrements showing in the placebo group. Multivariate analysis showed that depression was a major predictor of lower HRQL at all time points. Furthermore, fatigue was associated with lower PCS scores and insomnia was associated with lower MCS scores at certain points in time. Also, insomnia was found to be a major predictor of a larger decrement in HRQL during treatment.

Another part of the Younossi and colleagues (2014a) study showed the impact on HRQL of SOF and RBV for 12 weeks of treatment compared with the impact on PEG IFN + RBV for 24 weeks of treatment. There was no difference in clinical or demographic parameters between the two study arms at baseline and the last day of treatment (12 weeks for SOF + RBV and 24 weeks for PEG IFN + RBV). Both the physical and mental summary scores of SF-36 were lower in patients who had received IFN. The PEG IFN + RBV arm showed significantly lower HRQL scores for GH, VT, SF, RE, and RP (all $p < .05$), and a trend in lower scores for PF, BP, and MH ($p = 0.08$). The results showed that HRQL was significantly more impaired in the PEG IFN + RBV arm. Compared to baseline scores the impairment in the PEG IFN + RBV arm was significant in both PCS and MCS scores (both $p$
but there was only a modest decrement in the MCS score for the SOF and RBV arm. In addition, during treatment, receiving PEG IFN was an independent predictor of physical and mental health impairment.

The third part of the Younossi and colleagues (2014a) study compared the SOF + RBV treatment for 12 weeks and 16 weeks. There was no difference between the two arms at baseline or during treatment. There was no difference between those receiving treatment for 12 weeks compared to those receiving treatment for 16 weeks. Multivariate analysis showed that fatigue, insomnia and depression were important predictors of patient’s HRQL prior, during, and after treatment, and that anaemia and receiving interferon were predictors of decreased HRQL during treatment. Depression, fatigue and anxiety were found to be the major predictors of HRQL.

The fourth part of the Younossi and colleagues (2014a) study compared the impact of adding SOF to PEG IFN + RBV treatment. In both cases there was a rapid decrement in HRQL in SF-36 scores but the addition of SOF did not increase the decrement in HRQL score recorded for PEG IFN + RBV. Multivariate analysis showed that predictors of lower HRQL were anxiety, depression, fatigue and female gender.

In a more recent 2015 study of 3460 chronic hepatitis C patients (73.6% treatment-naive, 15.0% cirrhotic, 68.2% HCV genotype 1 and 20.1% genotype 3) HRQL data from nine multinational phase three trials of SOF- based study groups were evaluated. The evaluation comprised the following combinations with various durations: IFN + RBV± SOF, SOF + RBV± LDV, SOF± RBV and LDV± RBV, Participants completed the SF-36 HRQL prospectively at baseline, during treatment, and 12 and 24 weeks after treatment cessation. In the IFN+ RBV± SOF study groups there was a severe decrease in HRQL at the end of treatment compared to baseline and a moderate decrease in HRQL in SOF + RBV± LDV. In
contrast, improvements were noted in HRQL during treatment with SOF/LDV without RBV (Younossi, 2015).

3.2.5 **QOL AND HRQL POST HCV TREATMENT**

A study of 324 HCV patients investigated SVR and non-responders 24 weeks after treatment end (Ware et al., 1999). The study comprised two groups: one group were treated with IFN plus placebo and the other with IFN + RBV. Both groups were tested at baseline, and 12 and 24 weeks into treatment and 12 and 24 weeks after treatment end. The patients were assessed using the Health Quality of Life Questionnaire (HQLQ) containing the generic SF-36 measure plus three additional generic scales in addition to two hepatitis –specific scales (CHC health distress and CHC limitations). The study found that 24 weeks after treatment end, overall responders in both groups showed significant improvement on the measures of VT, SF, GH, HD, CHC Limitations and CHC Distress. HRQL showed improvement in 11 of 12 measures 24 weeks after treatment end compared to baseline HRQL scores. In contrast, the HRQL scores of non-responders decreased in 8 of 12 measures in the same comparative periods. The decrease in general health was significant ($p < .05$). In both cases HQLQ scores declined during treatment, but returned to or improved on baseline levels after treatment was stopped. It was also reported that at baseline HQLQ was significantly below mean population norms for SF-36 for five of the six SF-36 scales. The impact of SVR was most evident in the RP and GH domains.

Ware and colleagues (1999) also reported that for overall responders there was a decline from 53% at baseline to 33% at 24 weeks after treatment end for those reporting health-related limitations in social activities. There was no change in non-responders reporting of health-related limitations in social activities. In the SVR group, those responders who were discouraged because of their HCV infection, declined from 34% at baseline to 17% at 24 weeks after treatment end, with no change in non-responders. At 24 weeks after
treatment end the percentage of patients who achieved SVR, who reported no limitations in daily work because of hepatitis C, increased from 57% to 80%. Patients in the non-responder’s group were equally likely to report no limitations in daily work at baseline and at 24 weeks after treatment end.

There have been varied findings in the investigation of SVR and the effect on HRQL. McHutchison and colleagues (2001) reported that patients achieving SVR had significantly improved HRQL compared to non-responders with the impact of SVR being most evident in the RP and GH domains of the SF-36 measure. Two 2008 studies reported impairment of HRQL despite HCV patients achieving SVR. One of those 2008 studies reported that SF-36 scores were not correlated with either the presence or the level of HCV-RNA and that SF-36 scores were comparable in 555 HCV RNA-positive and 262 HCV RNA-negative individuals (Heibling et al., 2008). A second 2008 study (Pattullo, McAndrews, Mrkonjic, Damyanovich, & Heathcote, 2008) of 50 non-cirrhotic treatment-naïve HCV patients (41 of whom completed follow-up questionnaires) showed that there was no significant difference in the HRQL score between the 31 responders and 10 non-responders at baseline and post treatment. The researchers in that study concluded that successful viral clearance in patients with HCV resulted in modest, non-significant improvements in HRQL and there was minimal effect of HCV on CNS integrity and HRQL.

In the Hopwood (2009) qualitative study, twelve of twenty-seven patients treated with PEG IFN + RBV, and who achieved SVR, claimed their QOL had improved. Those participants who reported their QOL had not improved, reported being given unrealistic expectations about increased energy levels and improved QOL which should have resulted from clearance of HCV. Participants reported that the re-adjustment to life after treatment was difficult and exacerbated by persistent symptoms and not having treatment referrals, support information and advice.
The two Tillman and colleagues (2011) studies (Hannover and Liepzig) reported patients with SVR after IFN treatment were significantly worse than those patients with spontaneous clearance in the SF-36 domains of GH \( (p < 0.05) \) and VT \( (p < 0.05) \) and reported a trend in RE \( (p = 0.057) \). No other comparisons were significantly different. The researchers suggested HCV itself may not be involved in HRQL impairment but may induce in some patients a process which continues after viral clearance. In addition, it was found that HRQL may not always return to normal after the achieving of SVR.

The Hannover and Liepzig studies (Tillman et al., 2011) found that some HCV patients were significantly impaired in their well-being despite achieving SVR. In both the studies HCV patients who achieved SVR and non-responders scored significantly worse on the SF-36 measure than patients with spontaneous clearance.

The effect of SOF and RBV on HRQL in patients with CHC was investigated by Younossi and colleagues (2014a). CHC patients treated with SOF, PEG IFN, RBV or a placebo in different combinations and treatment durations were assessed using SF-36. No differences in MCS nor PCS scores were found at all time points. When the HRQL scores were compared to their respective baseline scores, HRQL decrements were found in patients receiving SOF + RBV in both PSC \( (p < 0.05) \) and MCS \( (p < .001) \). However, there was no decrement in the placebo group. The study found that patients returned to their baseline score by the end of either a 4 week or 12-week follow-up to treatment end. Furthermore, multivariate analysis showed that depression was a major predictor of lower HRQL at all times.

Another part of the Younossi and colleagues (2014a) study reported the impact on HRQL of SOF and RBV for 12 weeks of treatment compared with the impact of PEG IFN + RBV for 24 weeks of treatment. It was found that HRQL was significantly more impaired in the PEG IFN + RBV arm. The study found that patients in both treatment scenarios returned
to their baseline score and were no longer significant \((p > .05)\). Depression, insomnia, and fatigue were all associated with lower HRQL scores before, during and after the end of treatment. The third part of the study compared the SOF + RBV treatment for 12 weeks and 16 weeks. At SVR12 treated with SOF + RBV there was an improvement in HRQL compared to baseline. Also, there was no difference between those receiving treatment for 12 weeks compared to 16 weeks of treatment.

The fourth part of the Younossi and colleagues (2014a) study compared the impact of adding SOF to PEG IFN+ RBV therapy. At the end of the 12-week follow-up to treatment end all SF-36 scores returned to baseline levels \((p <.05)\). Multivariate analysis showed that fatigue, insomnia, depression were important predictors of patient’s lower HRQL.

The Younossi and colleagues (2015a) study investigated both IFN+RBV±SOF and IFN-free therapies with SOF and LDV. Their study showed that by week 12 post treatment, HRQL had returned to baseline in IFN+RBV±SOF group and improved in all IFN-free arms. Multivariate analysis showed a lower end of treatment HRQL was associated with IFN+RBV+SOF and a better HRQL at the end of treatment was associated with SOF/LDV. Furthermore, 12 weeks after the end of treatment SOF/LDV was associated with higher MH scores and those scores were maintained 24 weeks after the end of treatment. The researchers concluded that removing IFN and RBV led to a substantial improvement in the HRQL both during treatment and after the end of treatment (Younossi et al., 2015a). The implications of these findings are that there may be better patient experience and adherence to therapy with the elimination of IFN and RBV.

### Summary

Studies have shown that patients with HCV infection not only have impaired physiological outcomes, but may also have impaired QOL and HRQL. Patients with HCV have diminished QOL and HRQL when compared to controls without HCV. In addition,
some studies have shown that HCV patients who have achieved SVR have reported a better QOL and HRQL compared to those patients who have not achieved SVR. Some studies however have reported that QOL does not necessarily return to pre-treatment levels despite the patient achieving SVR.

Furthermore, studies have shown an association between fatigue, depression and anaemia and QOL and HRQL. Patient reports have shown a more pronounced effect on the VT, GH, PF, and SF scales of the SF-36 Health Survey which suggests that a wide range of factors have an effect on QOL and HRQL. Severity of liver disease and early histological changes have been shown to not be correlated to QOL and HRQL which tends to indicate that although liver damage associated with chronic infection (i.e. virus-related) may continue to impact HRQL, host-related factors may also reduce a patients’ HRQL despite the patient achieving SVR.

There is limited research available on HRQL and QOL during and post treatment boceprevir-based triple therapy. However, research involving SOF-based triple therapy indicates impairment in HRQL during treatment and a return to baseline levels of HRQL 12 months following the end of treatment.

Based on a review of the data and whilst PEG IFN + RBV and triple therapies are still being prescribed, it would be desirable continue with research with patients who have achieved SVR or are non-responders after PEG IFN + RBV therapy and triple therapy particularly in the follow up period. Further research in these factors will assist in fully understanding the mental and physical implications of HCV and treatment.

### 3.3 FATIGUE AND HCV

#### 3.3.1 INTRODUCTION

Fatigue is an overwhelming sustained sense of exhaustion and decreased activity for physical work at a usual level and is part of wide spectrum of diagnoses. Those diagnoses
range from fatigue being a psychological symptom in depression, anxiety and seasonal affective disorder (Terman et al., 1998) to being a full syndromal disorder in chronic fatigue syndrome (CFS). Fatigue is a subjective symptom and therefore is sometimes difficult to measure objectively (Volker, Kirchner, & Bock, 2016). Fatigue is also among the most frequent and disabling extrahepatic features of CHC (Barkhuizen et al., 1999). Kallman and colleagues (2007) differentiated chronic fatigue from CFS. Chronic fatigue was defined as fatigue persisting for more than 6 months. CFS in comparison is diagnosed as, in addition to fatigue, patients reporting at least four of the following CFS items: impairment of short-term memory, sore throat, tender lymph nodes, muscle pain, un-refreshing sleep, joint pain, headaches, and malaise lasting more than 24 hours after exertion, with these symptoms being present simultaneously for 6 months. According to Glacken and colleagues (2003), fatigue remains one of the least understood and neglected symptoms by health professionals and can be a precursor, a product, or a disease itself. Indeed, CFS is often misdiagnosed as depression (Griffith & Zraouf, 2007). It has been reported that depression can be manifested as extreme fatigue. Part of that depression is the inability to get things done due to being too tired (Tavakkoli, Ferrando, Rabkin, Marks, & Talal, 2013). Lewis and Wessely (1992) postulated that fatigue might be a victim of a variant of the Tudor-Hart’s inverse care law (Hart, 1971) in that the more ordinary a condition may appear, the less professional interest.

Research in other chronic illnesses such as multiple sclerosis (MS) has found that fatigue was strongly associated with depression after controlling for age, gender and mental status (Chwastiak et al., 2005). The Chwastiak and colleagues (2005) study also reported that in logistic regression analysis, patients with clinically significant depressive symptoms were more likely to report fatigue that was disabling and that anxiety and substance abuse disorders did not have the same association with fatigue. Fatigue may also arise from other
sources such as an individual’s medical history, other drug side effects and poor nutrition (Tavio, Milan, & Tirelli, 2002).

3.3.2 FATIGUE IN PATIENTS WITH HCV

Studies of patients with HCV show that fatigue is one of the most disabling and frequently reported symptoms of HCV. (Forton, Taylor-Robertson, & Thomas, 2003; Teuber et al., 2008). This finding has been supported by a number of studies which have investigated the relationship between fatigue and HCV (Barkhuizen et al., 1999; Hassoum, Willems, Deslauriers, Nguyen, & Huet, 2002; Hilsabeck, Webb, & Stern, 2007).

Glacken and colleagues (2003) conducted a qualitative study with 28 patients to ascertain the nature of HCV fatigue. The study identified two distinct classes of fatigue; chronic and idiopathic. Chronic fatigue was reported as being a permanent feature in patient’s lives. Patients talked about fatigue being “present even on wakening every morning”. For some the fatigue was a daily occurrence lasting a number of hours, whilst for others the fatigue was constant low-grade fatigue which was manageable if certain strategies were adopted. In contrast, the idiopathic fatigue was a recurring but transient fatigue which patients described as having two distressing features. First the fatigue was unpredictable in duration and occurrence, and second, the fatigue was intense. The intensity was reported as being so acute that “it had the ability to strip participants completely of their feeling of control”.

Glacken and colleagues (2003) also discussed the physiological and cognitive dimensions of fatigue in HCV patients. For the physiological dimension participants reported that “a feeling of heaviness was the over-arching way fatigue manifested itself”. Patients reported that at times they believed that they could “collapse with the weight of their bodies”. The physiological dimension of fatigue was also described as: “a terrible weakness”, being “discernible by its draining capacity”, being able to “sap participants of
their energy”, and robbing “participants of stamina, which subsequently curtailed their ability to engage in certain activities”. The researchers mentioned that patients reported that an aching sensation accompanied the fatigue so “that the fatigue had the capacity to activate or augment the severity of existing pain”. For the cognitive dimension, forgetfulness and lack of concentration appeared as the most universal aspects of fatigue.

Other aspects of fatigue reported by persons with HCV infection in the Glacken and colleagues (2003) study were affective sensation and severity. Participants reported a number of emotions in their fatigue such as anger, frustration, and anxiety. The researchers suggested that the fatigue experience could be the cause of “depressed mood”. Finally, it was reported that participants not only judged the severity of fatigue by its intensity, but considered fatigue severity as a combination of intensity, duration, and frequency. One participant stated being able to manage fatigue every day if it lasted for a few hours but added that “when it comes and doesn’t lift for days, I really feel defeated”.

A number of quantitative studies have investigated the incidence of fatigue in HCV infected patients. Hassoun and colleagues (2002) assessed the presence and severity of fatigue in 93 HCV-infected patients and reported 63% of those patients complained of fatigue. Piche and colleagues (2002) reported that 38 of the 78 CHC patients in their study listed fatigue as the worst and initial symptom of the disease. That study, using the Fatigue Impact Scale (FIS) (Fisk et al., 1994), found that fatigue scores were significantly higher in patients with HCV infection than in healthy controls ($p < .001$). Furthermore, it was found that women were significantly more likely to complain of fatigue than men ($p = 0.003$). The study found that leptin was increased significantly in CHC patients compared to controls ($p < 0.05$). Leptin is a peptide hormone that regulates food intake and energy expenditure. Elevated levels of leptin have been associated with steatosis. The study found that the fatigue experienced in HCV-infected persons may be due to elevated leptin levels. The study also
found no correlation between fatigue and age, resting energy expenditure, liver function tests, viral load or the METAVIR (a system used to assess inflammation and fibrosis by histological evaluation of a liver biopsy) score in CHC patients.

A study by Poynard and colleagues (2002) investigated 1,614 HCV-infected patients and found fatigue was reported by 53% of those patients and that fatigue was disabling in 17% of patients. Furthermore, Kramer and colleagues (2005) reported significant fatigue in 120 untreated HCV patients when compared with healthy controls. In that study, using the FIS measure, HCV patients reported on average significantly more fatigue (mean = 49 points) than the healthy control group (mean = 26 points). Kallman and colleagues (2007) reported that 95 (71%) of HCV patients in their study reported fatigue, compared to 53 (25%) of the healthy control participants. In that study 27% of the HCV patients and 11% of the controls were diagnosed with CFS. A 2008 German study reported results consistent with the 3 aforementioned studies. That study, based on completed questionnaires of 5,837 patients with chronic HCV, reported 45.6% of the patients felt continuously fatigued (Huppe et al., 2008). Heere and colleagues (2014) also reported higher scores in fatigue in HCV patients compared to healthy controls. Finally, in a qualitative study of 14 females with HCV-infection, participants attributed fatigue to the illness, expectation of chronicity, low control and fatigue-driven coping (Zalai, Carney, Sherman, Shapiro, & McShane, 2016).

Patients with a chronic illness such as HCV, who experience fatigue, may be unable to work full time or maintain acceptable work performance. Therefore, the economic impact on the individual can be significant. Furthermore, fatigue may mean that the individual reduces social activities which can result in depression and increased mood state disturbance.
3.3.3 FATIGUE AND RELATIONSHIP WITH OTHER PSYCHOLOGICAL SYMPTOMS AND WITH GENDER

There have been a number of studies which have investigated the relationship between fatigue and QOL and HRQL. Quesada and colleagues (1986) found that symptoms such as fatigue reported by HCV patients may strongly affect HRQL. Goh and colleagues (1999) reported that the perceived functional impact of fatigue was significantly higher in patients with chronic HCV genotype 1b compared to a healthy control group, but that fatigue was not related to the degree of HCV. A subsequent study, involving patients with chronic liver disease, found fatigue was strongly related to HRQL (Gutteling et al., 2006).

Furthermore, it has been reported that fatigue is an independent predictor of low HRQL (Kramer et al., 2005). Kramer and colleagues (2005) did, however, find that fatigue was not related to the severity of HCV infection. A study by Hilsabeck and colleagues (2005) showed the most significant predictor of fatigue in patients with HCV infection was poor social functioning. In a study of 50 patients with HCV infection, 14 of whom had current depressive disorders, it was found that the severity of depressive symptoms was highly correlated with fatigue severity. That study, which used the MAF Fatigue Questionnaire, found that measures of hepatic disease severity, IFN treatment and severity of comorbid medical illness, were not correlated to fatigue (Dwight et al., 2000). Other researchers have suggested that fatigue is more closely associated with depression than with HCV (Barkhuizen et al., 1999; Gutteling et al., 2006; Poynard et al., 2002; Rodger et al., 1999).

HCV-infected persons may not be able to continue their normal lifestyle due to fatigue and in some cases, will not be able to continue in full time employment or even part time employment. The inability to work or only working part time impacts on an individual’s quality of life (National Digestive Diseases Information Clearinghouse (NDDIC), 2006).
Fatigue and depression are often assumed to be comorbid conditions that are highly prevalent with chronic HCV infection or are consequences of chronic HCV infection (Gutteling et al., 2006; Hauser et al., 2004a; Karaivazoglou et al., 2010; Loria et al., 2014; Younossi, 2001). In patients with HCV, it has been reported that fatigue and depression were the most important independent predictors of patient reported outcome impairment (Dan et al., 2007; Younossi, Kallman, & Kincaid, 2007). Studies have shown that patient reported outcome impairment in HCV with early liver disease may be primarily due to the extra hepatic manifestations related to HCV, mainly fatigue and cognitive functioning (Strauss et al., 2014; Younossi et al., 2007).

The Hannover study, discussed previously under QOL/HRQL, found that HCV patients reported a trend towards higher fatigue scores ($p = 0.065$) compared to non-viral liver disease participants. The scores were significant in the dimension of social component of the FIS measure ($p = 0.018$). Patient groups with various liver diseases were not significantly different from each other in their total FIS scores. The “Hannover” study showed that patients who achieved SVR showed greater, but not significant, impairment in the FIS when compared to chronic patients (Tillman et al., 2011).

Carlson and colleagues (2004), while investigating sleep disorders in 80 HCV patients, found 70% of the patients reported significant fatigue. The study used the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) to measure fatigue. Heerren and colleagues (2014) found that fatigue and HRQL scores correlated with sleep disorders and daytime sleepiness. Kallman and colleagues (2007) reported that for both HCV-infected and non-infected control groups chronic fatigue was related to a decrease in HRQL, but neither chronic fatigue nor HRQL were associated with how HCV was transmitted, nor with age nor gender. Poynard and colleagues (2002) reported fatigue was associated, although only slightly, with gender and age, but was not associated with viral
factors. However, Piche and colleagues (2002) reported fatigue was associated with gender, with significantly more females than males reporting fatigue symptoms.

3.3.4 FATIGUE AND HCV TREATMENT

A study by Heathcote and colleagues (2000) reported that fatigue was the most commonly reported adverse event during HCV treatment. In their PEG IFN study 62% of patients reported fatigue during treatment. Poynard and colleagues (2002) reported that fatigue could affect PEG IFN + RBV treatment outcomes. The findings by Poynard and colleagues (2002) were supported by the research of Maddock and colleagues (2005) which found HCV patients were less likely to respond to therapy if they were experiencing severe fatigue. Furthermore, studies have shown fatigue and depression at the commencement of treatment are predictors for the failure to attain SVR in PEG IFN + RBV therapy. This failure may be attributable to treatment non-adherence (Bacon & McHutchison, 2005; Quelhas & Lopes, 2009).

Anaemia, a side effect of RBV, can lead to fatigue by reducing the blood’s capacity to carry oxygen. This may be one explanation of fatigue being a side effect of PEG IFN + RBV treatment. Studies have shown that depression and anaemia are the most important predictors of fatigue and HRQL (Dan et al., 2007; Kallman et al., 2007). In fact, Poordad and colleagues (2011) reported that fatigue was a common clinical adverse event in 60% of HCV patients undergoing boceprevir-based triple therapy. The Younossi and colleagues (2014a) study which compared SOF, PEG IFN + RBV and a placebo in various combinations found that fatigue was associated with lower Physical Component Summary scores in the SF-36 measure.

The relationship between fatigue and triple therapy has not been investigated to the same degree as PEG IFN + RBV. However, fatigue is a significant side effect of triple therapy with as many as 60% of patients reporting fatigue during triple therapy (Poordad et
Fatigue has been reported as one of the leading psychological adverse effects leading to discontinuation of boceprevir-based triple therapy (Kwo et al., 2010). A 2014 study of simeprevir plus PEG IFN +RBV reported that most of the fatigue reported by patients was attributable to the side effects of treatment, although at baseline those same patients did potentially experience some fatigue (Rosa et al., 2014). Furthermore, using the Chronic Liver Disease Questionnaire (CLDQ) (Younossi, Guyatt, Kiwi, Boparai, & King, 1999), it was reported that the fatigue domain was the most affected in patients on telaprevir-based triple therapy at weeks 4, 12 and 16 of treatment (Fagundes et al., 2015).

3.3.5 **FATIGUE POST HCV TREATMENT**

There are few studies which have used a fatigue specific measure to investigate fatigue and HCV posttreatment. Using both the FSS and SF-36 measures it was found that although PEG IFN affected fatigue during initial 12 to 24 weeks of therapy, there was an improvement in fatigue in patients achieving SVR (Bernstein, Kleinman, Barker, Revicki, & Green, 2002). In a study of simeprevir plus PEG IFN + RBV it was reported there was an improvement in fatigue after treatment end and patients achieving SVR had significantly lower FSS total scores than non-responders. That study did not report a comparison of fatigue at post treatment to baseline (Rosa et al., 2014).

A review of literature showed no other studies of HCV post treatment which used a specific fatigue measure. Those studies which did investigate fatigue relied on the SF-36 measure which included the Vitality (VT) scale as a measure of fatigue. The VT scale content included four questions related to whether the patient was feeling full of life, having a lot of energy, feeling worn out and feeling tired.

Ware and colleagues (1999), using the SF-36 measure, reported significant fatigue symptoms in patients post PEG IFN + RBV therapy. At end of treatment fatigue was above levels reported at baseline and even at 12 weeks after treatment end reported fatigue was still
above the fatigue reported at baseline. For those patients who achieved SVR baseline fatigue was reported by 66% of patients and by 40% of the same patients 24 weeks after the end of treatment ($p < .001$). Those patients who were non-responders (68%) reported fatigue at baseline and 64% reported depression 24 weeks after the end of treatment ($p < .01$).

The PEG IFN + RBV arm of the Younossi and colleagues (2014a) study, similar to the Ware and colleagues (1999), used the SF-36 measure. The study reported all scales of the SF-36 were significantly lower at treatment end compared to baseline. Also, at 12-week follow-up all SF-36 scales were significantly improved from treatment end but did not differ significantly from baseline. At 12-week follow-up, for all SF-36 scales, there was no difference for those patients who achieved SVR12 compared to non-responders.

Younossi and colleagues (2014a) also reported significant improvement in all SF-36 scales including the Vitality scale at 12-week follow-up to the end of treatment compared to pre-treatment in patients who achieved SVR with SOF-based triple therapy (either with PEG IFN + RBV (HCV genotypes 1, 4, 5, and 6)) or with SOF and ribavirin alone (HCV genotypes 2 and 3)). Of those who were non-responders at 12-week follow-up no meaningful improvement in fatigue was observed compared to baseline.

The Hepatitis C Trust (2007) web-based survey of 500 respondents who had undergone PEG IFN + RBV therapy reported fatigue in 72% of the participants within the first 6 month of treatment end follow-up. Furthermore 57% of participants reported fatigue from 6 months to 12 months of treatment end follow-up and 38% of participants reported fatigue 12 months or longer after treatment end. In this survey fatigue was the most frequently reported symptom post HCV therapy.

The Hopwood (2009) qualitative study of PEG IFN + RBV patients reported 6 of the 27 participants indicated fatigue was a post treatment symptom. Participants were interviewed via telephone or face-to face. Three of those 6 participants had achieved SVR.
after treatment end. Again, fatigue was the most commonly reported ongoing side effect and was reported as being a persistent physiological and psychological symptom which impacted on everyday activities such as sleep, socialising and employment. Weissenborn and colleagues (2009) review of fatigue and HCV reported that, even after successful HCV therapy, fatigue was present in about one third of patients.

3.3.6 SUMMARY

Studies to date have not clearly established the relationship between fatigue and liver disease (including HCV). However, fatigue does have debilitating effects on many HCV patients. Furthermore, studies have shown that fatigue is closely related to depression and QOL/HRQL. Also, the impact of fatigue on QOL/HRQL is significantly higher in HCV patients compared to healthy controls although studies have shown there is no relationship between fatigue and the severity of HCV.

Studies have also shown that IFN therapy exacerbates fatigue symptoms and fatigue has been reported as a clinical adverse event in up to 60% of HCV patients undergoing SOF-based triple therapy. A limited number of quantitative and qualitative studies have indicated that 24 weeks after the end of PEG IFN + RBV treatment a significant number of patients have reported ongoing fatigue symptoms. There are no quantitative studies which have investigated fatigue at three-month post boceprevir-based triple therapy. However, one quantitative study reported improved fatigue symptoms 12 weeks following SOF-based triple therapy.

3.4 SLEEP DISORDERS AND HCV

3.4.1 INTRODUCTION

The International Classification of Sleep Disorders, Third Edition (American Academy of Sleep Medicine, 2014) classifies sleep disorders into 8 major categories: insomnias, sleep-related breathing disorders, hypersomnias (excessive time spent sleeping or
excessive daytime sleepiness (EDS)) of central origin, circadian rhythm sleep disorders, parasomnias (abnormal movements, behaviours, emotions, perceptions, and dreams that occur while falling asleep, sleeping between sleep stages or arousal from sleep), sleep-related movement disorders, isolated symptoms, and other sleep disorders. The International Classification of Sleep Disorders also combines a symptomatic presentation (e.g. insomnia), with one organised partly on pathophysiology (e.g. circadian rhythms) and finally in part on body systems (e.g. breathing disorders) (American Academy of Sleep Medicine, 2014).

Excessive daytime sleepiness (EDS) (also known as hypersomnia) is one of the more common sleep disorders. A study of the Australian adult population found an overall standardised prevalence of EDS of 10.4% for men and 13.6% for women (Hayley et al., 2014). Furthermore, a 2008 poll conducted by the American Sleep Foundation found that 18% of respondents scored results which qualified them as excessively sleepy (Swanson et al., 2011). Australian population surveys have shown that 13%-33% of the adult population have regular difficulty either getting to sleep or staying asleep (Bartlett, Marshall, Williams, & Grunstein, 2008).

Daytime sleepiness is excessive when it causes a subjective complaint or interferes with function. EDS is defined as the inability to maintain wakefulness and alertness during major waking episodes of the day with sleep occurring unintentionally or at inappropriate times almost daily for at least three months (American Academy of Sleep Medicine, 2014). The International Classification of Sleep Disorders includes EDS as an essential feature of three diagnostic categories: narcolepsy, hypersomnia and behaviourally induced insufficient sleep syndrome (American Academy of Sleep Medicine, 2014). The Fatigue Severity Scale (FSS) is one of the subjective measures of sleep disorders and defines EDS as a score of $\geq 6.53$ reported by participants completing that measure (Krupp et al., 1989).
Insomnia is also one of the more common conditions reported by persons with sleep disorders (Schutte-Rodon, Broch, Buysse, Dorsey, & Sateia, 2008). Ohayon (2002), using the DSM-IV classification for insomnia, reported estimates of the prevalence of insomnia at 6% based on his 2002 review.

Insomnia may be classified firstly by cause; as primary insomnia (where the insomnia is the central problem, with no other illness or obvious cause) or as secondary insomnia (where insomnia is a symptom of or associated with other conditions including medical or psychiatric illness, substance abuse disorder or another sleep disorder) (American Academy of Sleep Medicine, 2014). Secondly, insomnia may be classified as acute or chronic. Short term or acute insomnia lasts less than four weeks. Chronic insomnia is defined as insomnia that lasts for four weeks or longer (American Academy of Sleep Medicine, 2014). Thirdly insomnia may be further defined by four sleep patterns: Sleep onset insomnia (difficulty falling asleep), sleep maintenance insomnia (e.g. the inability to stay asleep), terminal insomnia (waking up early and not being able to return to sleep) or non-restorative sleep (subjective feeling that sleep has been insufficiently refreshing, often despite the appearance of physiological normal sleep) (American Academy of Sleep Medicine, 2014).

In addition to EDS and insomnia, obstructive sleep apnea syndrome (OSAS) and sleep-related movement disorders (e.g. restless leg syndrome (RLS)) are common sleep disorders (American Academy of Sleep Medicine, 2014). Sleep apnea is characterised by repetitive closure of the upper airways during sleep. The main symptoms are intense snoring with breathing pauses and EDS. Also common are sleep-related movement disorders such as restless legs syndrome which has the symptoms of insomnia, and non-refreshing sleep, Furthermore, the body’s circadian rhythm dictates sleep patterns and any disruption of the circadian rhythm not only has physiological implications but also affects mood and cognitive abilities (American Academy of Sleep Medicine, 2014).
The negative effects of sleep disorders are numerous. Sleep disorders have been shown to significantly worsen many biological and psychological health issues and adequate sleep is necessary for the recovery from illness and for illness prevention. Sleep disorders can lead to lower QOL, depression, anxiety, lower cognitive function and social and family life problems. Furthermore, sleep disorders may cause problems in relationships, such as increased emotional reactivity, and the inability to process emotional information. Also sleep disorders may affect social problems causing reduced interactions with people (National Alliance on Mental Illness, 2016)

3.4.2 SLEEP DISORDERS AND PATIENTS WITH HCV

Studies have shown that patients infected with HCV report significant sleep disorders and that these sleeping disorders may occur prior to IFN treatment and in the absence of chronic liver disease. Sleep disorders in patients with HCV may cause exhaustion, increased irritability, and mood fluctuation (Kanwal et al., 2009; Shouval, 2014).

There are limited studies which have investigated sleep disorders in patients infected with HCV. Those studies which have investigated sleep report patients infected with HCV have sleep disorders such as EDS and dysfunctional nocturnal sleep which exist independent of antiviral therapy and before the onset of advanced liver disease (De Cruz et al., 2012). A number of physiological hypotheses have been suggested for the sleep disorders of HCV patients. These include: abnormal liver metabolism of plasma melatonin which affects sleep (Cordoba, Steindl, & Blei, 2009), dysregulation of histaminergic neurotransmission in the brain (histamine is involved in the regulation of the sleep-wake cycles) (Lozeva, Tuomisto, Tarhanen, & Butterworth, 2003) and dysregulation of serotonin and corticospinal tracts (Franco et al., 2008). However, research indicates that psychological factors may also play an important role in sleep disorders in patients with HCV infection.
A study by Carlson and colleagues (2004) investigated sleep disorders in 80 HCV patients. Of the 80 HCV patients, all of whom completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and FSS measures, 63% were identified as poor sleepers and 70% reported significant fatigue. Analysis showed that sleep quality did not differ according to the severity of liver disease. Furthermore, preliminary findings in that study suggested that sleep disorders may be independent of mood, depression and other psychiatric disorders in patients suffering from HCV infection. The study found a moderate relationship between global PSQI and FSS scores ($r = 0.50, p < .001$).

A further study of 264 HIV patients, 30 of whom were co-infected with HCV, showed that patients with both HIV and HCV infection reported poorer sleep than patients with HIV alone (Clifford, Evans, Yang, & Gulick, 2005). In addition, the study reported there were significant group differences in sleep quality and marginally significant differences in sleep disturbance. This study used the PSQI measure.

Lang and colleagues (2006), using both qualitative and quantitative studies, surveyed 188 treatment-naïve HCV patients and found that 65% reported having sleep problems. Sleep problems were among the top 10 symptoms reported by the patients in the study. Sleep problems were reported equally by males and females and were rated 8 on the visual analogue scale (VAS) (range 2 -10) and were the highest ranked score among the 21 symptoms reported. Similarly, Weissenborn and colleagues (2009) reported that approximately 50% of patients infected with HCV suffered from sleep disorders. While there was no gender difference in the reporting of sleep disorders, there was a gender difference in the reporting of depression, ‘physical tiredness’, “mental tiredness” and forgetfulness, which were all endorsed by women.

A 2014 German study, which included 25 female HCV patients and 22 age-matched female healthy controls, showed higher scores on the PSQI and the Epworth sleepiness scale
(ESS) measures for the HCV patients compared to the control group (Heeren et al., 2014). The ESS measures daytime sleep. Actigraphy showed higher nocturnal activity and dysfunctional sleep in the HCV patients. However, 24-hour activity level did not differ between groups. The PSQI mean scores were 13 (range 8.25-16) and 5 (range 3 – 7) for the HCV patients and control groups respectively ($p <.001$). In the study, fatigue and HRQL scores correlated with sleep disorders and daytime sleepiness. The study also found that sleep-related problems occurred early in the course of liver disease. The researchers of this study reported the results confirmed that sleep disorders should be regarded as an extrahepatic manifestation of HCV.

Yoh and colleagues (2016) in their study comparing CHC patients treated with IFN-based therapy and DAAs measured sleep characteristic at baseline using the PSQI and actigraphy. Interestingly the PSQI mean scores at baseline for the two CHC patient groups in that study were 3.5 (range 1-15) and 4 (range 0-12) both of which are lower than mean score of 5 (range 3-7) reported for healthy controls in the Heeren and colleagues (2014) study. A PSQI mean score for normal sleep is 2.67 ($SD = 1.70$) (Buysse et al., 1989).

Finally, a study found that patients with a history of chronic HCV infection without overt cirrhosis may develop a disrupted circadian rhythm. A disrupted circadian rhythm is associated with altered sleep patterns, insomnia, fatigue, depression and reduced QOL. Patients in this study showed increased nocturnal activity. However, no correlation could be established between fatigue and sleep pattern abnormality and 24 hour activity level (Shouval, 2014).

3.4.3 SLEEP DISORDERS AND PATIENTS WITH CIRRHOSIS OF THE LIVER

There have been limited studies on sleep disorders and patients with liver cirrhosis. One study compared 20 patients with liver cirrhosis with 20 healthy controls using a sleep questionnaire and actigraphy over 5 consecutive days. The study found dysfunctional sleep
patterns, higher nocturnal activity and reduced physical activity over a 24 hour period in the patients with liver cirrhosis compared to the control group (Cordoba et al., 1998). However, one study found that night-time sleep disorders did not correlate with neuropsychiatric impairment in patients with cirrhosis (Montagnese, Middleton, Skene, & Morgan, 2000).

Another study, which compared 178 patients with liver cirrhosis with 178 healthy controls, found that patients with cirrhosis showed significantly higher daytime sleepiness and dysfunctional sleep including trouble falling asleep and frequently waking up during the night. Also daytime sleepiness and nocturnal sleep disorders were more evident in patients with minimal hepatic encephalopathy in contrast to other cirrhotic patients (Mostacci et al., 2008).

A further study by Montagnese and colleagues (2009) assessed 87 patients with liver cirrhosis with and without minimal or overt hepatic encephalopathy and 19 healthy controls. The study found patients reported higher scores in the PSQI and the Epworth sleepiness scale (ESS) than the control group, thus indicating greater sleep disorders. In the study almost 70% of patients were classified as poor sleepers using the PSQI measure. However, this study also showed there was no significant correlation between both the PSQI and ESS scores and the presence of hepatic encephalopathy. These findings confirmed those found in the Cordoba and colleagues (1998) study which showed that cirrhotic patients had trouble falling asleep and also had dysfunctional sleep behaviour. The results of these studies show that a significant number of cirrhotic patients suffer from daytime sleepiness, insomnia, and nocturnal sleep disorders. However, there is varying evidence as to whether these variables are correlated to the severity of cirrhosis or not.

A cross-sectional study by AL-Jahdali and colleagues (2014) investigated 200 stable patients with confirmed liver cirrhosis. For the participants in the study, HCV was the most common cause (60.2%) of liver cirrhosis. The study found that the presence of insomnia was
higher in HCV (51.7%) patients compared to HBV (36.8%) patients and patients with other hepatitis diseases (15%) \( (p = .001) \). The study indicated a significant relationship between severity of liver cirrhosis and the presence of insomnia and found that insomniac patients were significantly older than non-insomniac patients \( (61.6, SD=12 \text{ years vs } 57.0, SD=12 \text{ years respectively, } p<.01) \). Multivariate analysis showed that HCV, coffee intake, excessive daytime sleepiness and short sleep duration were the most strongly associated with the presence of insomnia.

Besides insomnia the other two significant sleep disorders reported by HCV patients with cirrhosis are RLS and obstructive sleep apnea (OSA). The Restless Legs Sleep Questionnaire (Allen & Earley, 2001) is one measure used to identify RLS. The Berlin Questionnaire is one measure used to identify sleep apnea syndrome (Netzer, Strohs, Netzer, Clark, & Strohl, 1999). In a study with 141 patients with chronic liver disease who were seen in an academic-based tertiary care hepatology clinic, it was found that 62% of respondents indicated RLS. The prevalence of RLS did not differ by gender (Franco et al., 2008). It was also found that OSA was a complication of cirrhosis (Crespo, Cifrian, Pinto, Jimenez-Gomez, & Pons-Romero, 2003) and that as the severity of cirrhosis increased so did the presence of OSA (Ogata, Nomura, Nakaya, & Ito, 2006). Another study found that the presence of OSA was similar in cirrhotic patients and non-cirrhotic patients with chronic viral hepatitis (Nikaina, Pastaka, Zachou, Dalekos, & Gourguolianis, 2006).

3.4.4 SLEEP DISORDERS AND RELATIONSHIP WITH OTHER PSYCHOLOGICAL SYMPTOMS AND WITH GENDER

The importance of sleep to a person’s psychological wellbeing has been well documented. In the general population sleep disorders impact negatively on HRQL (Baldwin, Kapur, Holberg, Rosen, & Nieto, 2004; Iliescu et al., 2002) and sleep disorders have been associated with many factors than impair an individual’s HRQL. Studies have shown that
sleep disorders are associated with pain (Smith, Perlis, Smith, Giles, & Carmody, 2000), impairment of cognitive functioning (Baldwin et al., 2004), immune dysfunction (Dinges, Douglas, Hammarman, Zaugg, & Zapor, 1995), and metabolic and neuroendocrine dysfunction (Spiegel, Lepoult & Canter, 1999). Furthermore there is an established relationship between sleep disorders and QOL in the medically ill population (Musci et al., 2005).

Recent research suggests that sleep disorders may have additional serious consequences such as exhaustion, increased irritability, mood swings, depression, anxiety, anger, reduced concentration and cognitive abilities, decreased productivity and creativity, daytime sleep and metabolic abnormalities (Durmer & Dinges, 2005; Shouval, 2014). Persons with generalised anxiety disorder (GAD) are approximately three times more likely to report difficulty initiating sleep, problems maintaining sleep and early morning awakening, and are six times more likely to experience non-restorative sleep (Roth et al., 2006).

Carmichael and Reis (2005, p.526) stated that: “Identifying psychological factors that aid or hamper sleep adds to understanding of the mechanisms by which dispositional factors promote health and prevent illness”.

In HCV research insomnia has been found to be a major predictor of a larger decrement in HRQL and has been reported as being associated with lower Mental Component Summary scores in the SF-36 at certain points in time. (Younossi et al., 2014). Carlson and colleagues (2004), while investigating sleep disorders in 80 HCV patients, found that 70% reported significant fatigue. Also, Heerren and colleagues (2014) found that fatigue and HRQL scores correlated with sleep disorders and daytime sleepiness. Similarly, Montagnese and colleagues (2009) study reported that nocturnal sleep disturbance and evening preference were independent predictions of QOL. Furthermore, Poordad and
colleagues (2011) reported that sleep disorders may predict the onset of Major Depressive Disorder (MDD) in patients undergoing IFN therapy.

Excessive daytime sleepiness (EDS) is more common in those reporting symptoms of depression or anxiety disorders (Slater & Steier, 2012) and significantly impacts on an individual’s QOL (Baldwin et al., 2004; Slater & Steier, 2012). Baldwin and colleagues (2004) also reported EDS has been associated with poorer health outcomes, poor cognition, and greater limitations in instrumental activities of daily living.

Most studies investigating EDS show an equal gender ratio or a female predominance of up to 1:2 (Hillman, Murphy, & Pezzullo, 2006). Furthermore, a study of the Australian adult population found an overall standardised prevalence of EDS of 10.4% for men and 13.6% for women (Hayley et al., 2014). Baldwin and colleagues (2004), after adjusting for possible confounding variables identified in bivariate analysis, reported male to female odds ratios for sleep onset insomnia (2.04), sleep maintenance insomnia (1.60), terminal insomnia (1.46) and non-restorative sleep (1.48). Furthermore, men to women ratios for insomnia symptoms increase with age, the ratio of men to women being 1:7 after 45 years of age (Ohayon, 2002).

3.4.5 SLEEP DISORDERS AND HCV TREATMENT

The study of sleep disorders in HCV patients is important as inadequate sleep may lead to poor treatment outcomes (Kanwal et al., 2009). Despite the effect of sleep on treatment outcomes there is limited research on sleep disorders with HCV patients treated with PEG IFN + RBV therapy or triple therapy. A study in 2000 found that 22% of patients undergoing IFN therapy and 19% of patients undergoing PEG IFN therapy reported sleep disorders (Heathcote et al., 2000). A subsequent study found that insomnia was reported by 23% of patients being treated with IFN and 33% of patients being treated with PEG IFN (Reddy et al., 2001). A further study investigated sleep and depression during IFN treatment
and found that sleep quality was better in CHC patients with a particular genotype of the serotonin transporter length promotor region that was associated with a lower rate of MDD. The researchers suggested there was a possible mediational role of sleep quality in resilience to MDD (Lotrich et al., 2009).

A 2009 study found that poor sleep quality was associated with subsequent depression during PEG IFN + RBV therapy and may predict the onset of MDD in CHC patients undergoing PEG IFN + RBV therapy (Prather, Rabinovitz, Pollock, & Lotrich, 2009). However, depression was found not to be associated with changes in sleep quality. The study used the PSQI to measure sleep and a semi-structure interview to diagnose MDD.

Furthermore, the Poordad and colleagues (2011) study of untreated chronic HCV genotype 1 patients undergoing boceprevir-based triple therapy reported that insomnia was a clinical adverse event in 34% of patients and that sleep disorders may predict the onset of MDD in patients undergoing therapies with IFN.

The Yoh and colleagues (2016) study reported the PSQI mean scores and actigraphy scores at baseline and at four weeks after the commencement of treatment for HCV-infected patients undergoing two types of therapy. The two therapies were simeprevir (SMV) triple therapy (group A) and IFN-free DAA therapy (group B). In group A, comprising 31 patients, there were significant increases in sleep disorders, measured by the PSQI, from baseline ($M = 3.5$, range 1-15) compared to four weeks after treatment commencement ($M = 5$, range 1-13; $p < 010$). In group B, comprising 41 patients, there was no significant difference in reported PSQI mean scores between baseline compared to four weeks after treatment commencement. In group A there were significant increases in sleep disorders in three of the five variables measured by actigraphy. The three actigraphy variables showing significant change were Wake after sleep onset, Activity index and Wake episodes. The two actigraphy variables showing no significant change were Sleep onset latency and sleep episodes. In group B, there
was no significant difference in reported PSQI mean scores between baseline compared to four weeks after treatment commencement. In group B only one actigraphy variable (sleep episodes) showed significant change between baseline compared to 4 weeks after treatment commencement.

3.4.6 SLEEP DISORDERS POST HCV TREATMENT

A review of literature indicated there was no specific research on sleep disorders of HCV patients following the end of treatment with PEG IFN + RBV therapy nor triple therapy. The continuance of sleep disorders after HCV therapy has been reported by patients in a qualitative study although the reported prevalence of sleep disorders was less than that of fatigue (The Hepatitis C Trust, 2007). The Hepatitis C Trust (2007) web-based survey of 500 respondents who had undergone PEG IFN + RBV therapy reported insomnia in 41% of the participants within the first 6 month of treatment end follow-up. Furthermore 27% of participants reported insomnia from 6 months to 12 months of treatment follow-up and 18% of participants reported insomnia 12 months or longer after treatment end. The survey reported unrefreshing sleep in 43% of the participants within the first 6 month of treatment end follow-up. Furthermore 33% of participants reported unrefreshing sleep from 6 months to 12 months of treatment end follow-up and 26% of participants reported unrefreshing sleep 12 months or longer after treatment end. In addition, the survey reported “sleep a lot” as a problem in 27% of the participants within the first 6 months of treatment end follow-up. Furthermore, 22% of participants reported “sleep a lot” from 6 months to 12 months of treatment end follow-up and 26% of participants reported “sleep a lot” 12 month or longer after treatment end. The Hopwood (2009) qualitative study of PEG IFN + RBV patients reported 1 of the 27 participants, who had not achieved SVR after HCV treatment, indicated that sleep disorder was a post treatment symptom.
3.4.7 SUMMARY

Despite the reporting of the importance of sleep for a patient’s physiological and psychological wellbeing, sleep disorder in HCV patients is poorly researched and poorly understood. Research has shown that sleep disorders can occur prior to therapy and prior to the onset of advanced liver disease and during PEG IFN + RBV therapy and triple therapy. A review of literature showed a paucity of published studies of the relationship between sleep and PEG IFN + RBV therapy and triple therapy. The research that is available does however show that insomnia is an adverse effect in both therapies. Two qualitative studies have reported ongoing sleep disorders not only by non-responders but also by those patients achieving SVR. A review of research indicates that no quantitative research has been conducted post treatment for neither PEG IFN + RBV therapy or triple therapy.

The underlying mechanisms of sleep behaviour in HCV patients are not yet clearly defined and may involve a number of factors. Future research on the effects on the brain of HCV infection, HCV therapy, both during and post therapy, may deliver important data on the nature of sleep disorders in HCV patients. Furthermore, research into the nature of sleep disorder, both physiological and psychosocial, would provide important information on the course of HCV disease, aid in better adherence to therapy and allow for appropriate supportive care.

3.5 MOOD STATES AND HCV

3.5.1 INTRODUCTION

The current study measured mood state disturbances. Mood states are transient, fluctuating feelings and enduring affect states (Heuchert & McNair, 2012). To objectively measure mood states Heuvhart and McNair (2012) use 6 scales: anger-hostility (AH), confusion-bewilderment (CB), depression-dejection (DD), fatigue-inertia (FI), tension-anxiety (TA) and vigour-activity (VA). Affect states may be positive or negative. Positive
affect states refer to the subjective moods such as joy, interest and alertness (Miller, 2011). Negative mood states involve poorer self-concept and a variety of negative emotions including anger, contempt, disgust, guilt, fear and nervousness (Stringer, 2013). Mood states, unlike personality traits, are thought to be transitory and specific to a situation. Mood states can be measured for recent prolonged periods such as the past several months (Heuchert & McNair, 2012). Not only depression but also the emotional state of the patient can modify neurocognitive function (Lezak, Howieson, Bigler, & Tranel, 2012).

3.5.2 MOOD STATES AND PATIENTS WITH HCV

There is little research available on patients’ mood states and HCV. Baseline mood status may be a predictor of IFN-induced depression (Constant et al., 2005). The study by Constant and colleagues (2005) found that IFN-induced mood disorders was frequent (32%) in patients with chronic HCV. It was reported that a history of psychiatric disorders and baseline-elevated scores on scales of depression as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and anxiety, as measured by the State Trait Anxiety Inventory (STAI), were significant predictors of IFN-induced depression.

3.5.3 MOOD STATES AND HCV TREATMENT

While most studies of the side effects of PEG IFN + RBV have investigated depression, there have been a few studies which have investigated a wider range of possible side effects. Studies have shown that patients treated with PEG IFN +RBV reported increased impatience, irritability and hostility (Fried et al., 2002; Manns et al., 2001). Kraus and colleagues (2003) reported a significant increase in anger and hostility during PEG IFN + RBV therapy. Furthermore, irritability, anger and hostility and manic and hypomanic episodes have been commonly reported by persons undergoing PEG IFN +RBV therapy (Constant et al., 2005). The Constant and colleagues (2005) study included 93 previously IFN alpha-naïve patients treated with PEG IFN + RBV. Psychiatric problems (which included
mood states) occurred in 30 patients. In the 30 patients there were reported 18 cases of irritable manic/hypomanic episodes. Those 18 cases, however, did not meet the usual DSM-IV criteria for major depressive disorder (MDD). In addition, 15 of those 18 cases reported irritable mood, racing thoughts, distractibility, transient psychomotor agitation, and insomnia, and were diagnosed as hypomanic. Interestingly, despite those cases presenting hypomanic symptoms, patients exhibited reported severe fatigue, a symptom that is not a criterion for the diagnosis of hypomania. Furthermore, of the 30 patients reporting mood disorders, there were 12 cases of depressive mixed states. Neurovegetative symptoms appeared within 4 weeks in most patients. In patients who developed mood disorders, sadness and depressive thoughts were present but low in severity. However, in those patients who did develop mood disorders, inner tension and anxiety increased significantly over time. The study concluded the IFN-alpha-induced mood disorders are common and consist of an overlap between depressive and manic symptoms rather than mere depression. A review of the literature showed no studies which have investigated triple therapy and the effect on mood states.

3.5.4 MOOD STATES POST HCV TREATMENT

A review of the literature found no quantitative research which have addressed mood states in PEG IFN + RBV therapy or triple therapy post treatment. The Constant and colleagues (2005) study investigated mood states up to the first 12 weeks of therapy but did not investigate mood states post treatment. The Hepatitis C Trust (2007) web-based qualitative survey of 500 respondents who had undergone PEG IFN + RBV therapy reported mood swings being a significant side effect in 48% of the participants within the first 6 month of follow-up to treatment end. Furthermore, 35% of participants reported mood swings from 6 months to 12 months follow-up to treatment end, and 23% of participants reported mood swings 12 month or longer after follow-up to treatment end.
The Hopwood (2009) qualitative study of PEG IFN + RBV patients reported patients having difficulties with emotion and strained relationships after the end of treatment and that these factors were exacerbated by lack of referrals, support, and medical care for their ongoing symptoms. For patients who were non-responders, the study reported patient anger at the treatment study group for making them feel so terrible for so long with no gain.

### 3.5.5 SUMMARY

Mood states are transient, fluctuating feelings and enduring affect states. And are unlike personality traits. There is little research on mood states in HCV-infected persons but mood states may be a prediction of IFN-induced MDD. The few studies which have investigated mood states during PEG IFN + RBV therapy showed persons who were identified with the side effects of mood states exhibited irritability, anger, hostility, and manic and hypomanic episodes. The review of literature showed no quantitative studies which have investigated mood states post HCV therapy. However, two qualitative studies reported ongoing mood swings post PEG IFN + RBV therapy.

### 3.6 DEPRESSION AND HCV

#### 3.6.1 INTRODUCTION

Symptoms of major depressive disorder (MDD) are: sad or depressed mood, loss of interest or pleasure in activities, significant change in weight, sleep disturbance, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, problems thinking, concentrating or making decisions and recurrent thoughts of death (American Psychiatric Association, 2013).

#### 3.6.2 DEPRESSION AND PATIENTS WITH HCV

Relatively little is known about the psychological factors in the aetiology of depression in patients with HCV infection despite the recognition of depression in patients with HCV infection and those patients undergoing HCV therapy. Because there are various
factors contributing to MDDs, establishing a causative relationship between HCV infection and depression is difficult. Potential mechanisms have been identified which connect HCV infection and depression (Cutler, 2009). Firstly, it has been suggested that psychiatric disorders such as depression may lead to high risk behaviour such as injecting drug use which increases the probability of an individual contracting HCV. Secondly, it has been theorised that the physical symptoms of HCV reduce the QOL of the patient which may then lead to depression. (Vignau, Karila, Costisella, & Canva, 2005). A third theory states that there is a potential for the HCV to affect the CNS and cause the onset of depression (Forton, Karayiannis, Mahmud, Taylor-Robertson, & Thomas, 2004; Wilkinson, Radkowski, & Laskus, 2009). A recent study concluded that HCV-infected blood cells enter into and reside in the brain and affect brain cells (Weissenborn et al., 2009). Finally, the psycho-spiritual theory purports that HCV causes depression because those affected feel they lack control over the ability to recover from the illness. This later mechanism may occur when the patient is informed that the HCV is incurable, when the patient has doubts about ridding themselves of the HCV and when they feel their condition is worsening due to experiencing the severe side effects from drug therapy (Golden, O'Dwyer, & Conroy, 2005).

Particular studies that have investigated patients diagnosed with HCV include a 2008 study that showed this population has a higher frequency of unrecognized psychiatric comorbidity (Batista-Neves et al., 2008). Zignego and colleagues (2007) reported psychopathology in HCV patients before treatment, with depression being reported in 69.7% of HCV patients compared to 15.4% in a control group. Similarly, the Carta and colleagues (2007) study found an association between HCV and depression and that this association was independent on IFN treatment and was not influenced by substance or alcohol abuse.

Furthermore, a recent cross-sectional study of 81 HCV-infected patients with mild liver disease, but who were not undergoing HCV treatment, found a significantly higher level of
depression ($p = .001$) than in the general population (Erim et al., 2010). That study found that women, persons who were single, and persons with a shorter period after first diagnosis, showed significantly higher levels of depression.

3.6.3 DEPRESSION AND RELATIONSHIP WITH OTHER PSYCHOLOGICAL SYMPTOMS AND WITH GENDER

Fatigue and depression are often assumed to be comorbid conditions that are highly prevalent with CHC or are consequences of chronic HCV infection (Gutteling et al., 2006; Hauser et al., 2004a; Loria et al., 2014; Younossi, 2001). In patients with HCV, it has been shown that fatigue and depression were the most important independent predictors of patient reported outcome impairment (Dan et al., 2007; Younossi et al., 2007). In a study of 50 patients with HCV infection, 14 of whom had current depressive disorders, it was found that the severity of depressive symptoms was highly correlated with fatigue severity (Dwight et al., 2000). Other researchers have suggested that fatigue is more closely associated with depression than with HCV (Barkhuizen et al., 1999; Gutteling et al., 2006; Poynard et al., 2002; Rodger et al., 1999). Poordad and colleagues (2011) reported that sleep disorders may predict the onset of MDD in patients undergoing IFN therapy. Similarly, Shouval (2014) reported that one of the consequences of sleep disorders was depression. Finally it has been reported that in multivariate analysis, depression was one of the important predictors of HRQL prior, during and after HCV treatment (Younossi et al., 2014a).

Erim and colleagues (2010) found that gender and a sense of coherence predicted depression scores in HCV patients ($R (22) = .42, p < .001$). The study found that the expression of depression in HCV patients was modulated not only by biological factors, but also by psychological factors. The study found that a sense of coherence was a protective factor in the development of depression and concluded that the high prevalence of depression
and anxiety in HCV patients not receiving antiviral treatment justified psychosocial screening.

3.6.4 **DEPRESSION AND HCV TREATMENT**

The relationship between Ribavirin (RBV) and depression was investigated in a study which used RBV as a monotherapy for HCV treatment (Bodenheimer et al., 1997). That study reported an association between RBV and increased depression in HCV patients. Also a 2003 prospective study, which evaluated patients taking IFN with or without RBV, found rates of depression were increased in the combined IFN + RBV treatment patients compared to IFN monotherapy patients (Kraus et al., 2003). The Raison and colleagues (2005a) study was the first to directly investigate depression and RBV. It was found weight-based RBV therapy significantly increased the risk of developing depression.

Early studies involving HCV, depression and patients receiving PEG IFN + RBV have shown there was depression in 16% of patients (Davis et al., 1998). A further study by McHutchison and colleagues (1998) showed that 36% of patients being treated with IFN + RBV showed symptoms of depression, while 32% of patients showed irritability and 18% showed anxiety. A 2001 study involving patients treated with PEG IFN + RBV reported depression in 31% of patients and anxiety in 35% of patients (Manns et al., 2001). In the following year a study of patients being treated with PEG IFN + RBV reported depression in 22% of patients and anxiety in 21% of patients (Fried et al., 2002). A subsequent study a 2003 prospective observational study of patients undergoing PEG IFN + RBV treatment showed that 48% of patients, who were not in psychiatric care at baseline, required treatment for depression and 23% of patients developed symptoms which were consistent with major depression. The study found that treatment with anti-depressants was helpful in stabilising the effects of depression and allowed the patients to continue with the therapy (Dieperink et al., 2003).
A further study by Raison and colleagues (2005a) reported that moderate to severe depression occurred frequently in patients undergoing PEG IFN + RBV treatment. That study also reported that development of depression was predicted by baseline depression scores and higher doses of RBV. The study found that factors which did not predict the development of depression during PEG IFN + RBV therapy (controlling for baseline Zung Self-Rating Depression Scale (SDS)) included gender, age, viral genotype, history of substance abuse, history of depression, antidepressant use or the need for dose reduction in either PEG IFN + RBV or RBV alone. Although MDD was controlled for in the regression model mentioned above, patients with a depressive history showed a significantly higher rate of moderate to severe depressive symptoms during PEG IFN + RBV therapy than patients with no history. When logistic regression analysis was repeated, without controlling for baseline SDS index score, a history of MDD became a significant prediction of moderate to severe depression during PEG IFN + RBV therapy. This study was a prospective cohort study and the relationship between depression and viral clearance was examined retrospectively. In addition, anti-depressant use and treatment adherence was not controlled. It is interesting to note that baseline depression scores in the study were similar to those in the general population. These baseline scores, showing that depression scores of the HCV patients were similar to the general population, are contrary to other research findings both prior (Lee, Jamal, Regenstein, & Perrillo, 1997; Malaguarnera et al., 1998; Singh, Gayowski, Wagener, & Marino, 1997) and subsequent (Batista-Neves et al., 2008) to the Raison and colleagues (2005a) study.

A number of studies have investigated the relationship between the variables of gender, a history of substance abuse and the development of depression during both non-pegylated and PEG IFN + RBV treatment. In a 2005 study of patients undergoing PEG IFN + RBV, gender did not show as a predictor of depression during treatment (Raison et al.,
Studies have shown that antidepressants effectively reduce IFN induced depressive symptoms, whether the antidepressants are administered before, or during treatment (Kraus, Schafer, & Scheurlen, 2001; Musselman et al., 2001; Raison et al., 2007). Similar results have been found for patients being treated with PEG IFN + RBV (Raison et al., 2005a).

A number of studies have investigated the relationship between depression and SVR. It has been reported that psychiatric comorbidity may not only be the main cause of poor compliance, therapeutic discontinuations and treatment contra-indication, but may also influence IFN response rates (Lang et al., 2003). A 2004 prospective study using the Beck Depression Inventory (BDI) found that the IFN response rate in patients who developed IFN induced MDD, and were treated with antidepressants, were significantly higher than those patients who did not develop depression. The study concluded that findings suggested IFN-alpha-induced major depression may be a predictor of a positive response to IFN-alpha therapy or an indication of optimal dosing (Loftis et al., 2004). In the study 13 of the 39 participants developed IFN induced MDD and were treated with the anti-depressant citalopram. The IFN response rate in those 13 patients who developed IFN induced MDD were significantly higher than the 26 patients who did not. The researchers noted that most of those 13 patients were able to remain on the full course of therapy and showed improved EVR and SVR compared to the other 26 patients.

Raison and colleagues (2005b) studied 102 patients (51.0% who had a history of drug abuse) being treated with PEG IFN + RBV. Patients were evaluated at baseline, and after weeks 4, 8, 12 and 24 of treatment using the SDS. The primary finding of this study was that patients who developed significant increases in symptoms of depression while being treated
with PEG IFN + RBV were less likely to have viral clearance after 24 weeks of therapy, thus highlighting the importance of identifying and treating depressive symptoms in this patient population. The patients in the Raison and colleagues (2005b) study were not treated with antidepressants. The identifying and treatment of depressive symptoms is especially important in light of the findings of the Loftis and colleagues (2004) study.

The results of the Raison and colleagues (2005b) study were consistent with the findings of another 2005 study which found a relationship between fatigue (a symptom of major depression) and a reduction in viral clearance (Maddock et al., 2005). Further to these studies it was reported patients who had a history of depression and were not taking antidepressants had a significantly lower SVR rates as well as higher rates of discontinuance than those taking antidepressants (Alvarez-Uria, Day, Nasir, Russell, & Vilar, 2009). Another study observed that a higher score on the Major Depression Inventory (MDI) was related to the onset of depression during PEG IFN + RBV treatment (Leutscher, Lagging, & Buhl, 2010).

Most research on the adverse effects of triple therapy has concentrated on physiological effects or HRQL. Kow and colleagues (2010) reported that depression was one of the common psychological adverse effects reported by patients as the reason for withdrawal from triple therapy.

3.6.5 **DEPRESSION POST HCV TREATMENT**

Most studies of PEG IFN + RBV therapy and triple therapy have investigated depression during treatment and studies investigating post treatment depression are more limited. The Hepatitis C Trust (2007) web-based survey of 500 respondents who had undergone PEG IFN + RBV therapy reported depression as a significant side effect in 56% of the participants within the first 6 month of treatment follow-up. Furthermore, 45% of participants reported depression from 6 months to 12 months of treatment end follow-up and
32% of participants reported depression after 12 months or longer after treatment end. The Hopwood (2009) qualitative study of PEG IFN + RBV patients reported that two of the 27 study participants reported depression after treatment. One of the two participants achieved SVR after PEG IFN + RBV therapy. Also 8 of the participants reported cognitive effect which included depression in the definition of cognitive effect.

3.6.6 SUMMARY

Research has shown there is a statistically higher prevalence of depression in patients with HCV infection compared to the general population. Psychological factors have been recognised in the causative relationship between HCV infection and depression. Studies have also shown the statistically high incidence of depression in HCV patients undergoing PEG IFN + RBV treatment and that this treatment may induce depression in patients. Research also indicates that patients who develop significant increases in symptoms of depression while on PEG IFN + RBV treatment may be less likely to achieve SVR. Finally, depression has been reported post HCV treatment by both treatment responders and non-responders. A review of literature reveals a paucity of research investigating the relationship between depression and triple therapy, however in the research that is available it is reported that depression is a significant adverse effect of triple therapy.

3.7 ANXIETY AND HCV

3.7.1 INTRODUCTION

The term anxiety may be defined in terms of the two constructs of state anxiety and trait anxiety (Endler & Kocovski, 2001). State anxiety is commonly defined as an unpleasant emotional arousal arising from threatening demands or dangers. A prerequisite for the experience of state anxiety is a cognitive appraisal of a threat (Endler & Parker, 1991). Stressful situations or encounters such as illness, disease or medical treatment may lead to increased levels of state anxiety. The other construct in the definition of anxiety, trait anxiety,
is defined as the existence of stable individual differences (Spielberger, 1983). Trait anxiety may also be referred to as enduring emotional distress, trait negative affect or neuroticism. It is a stable personality trait which is difficult to change (Lazarus, 1991). In explaining the multidimensionality of trait anxiety, Endler and colleagues (1991) listed four facets of trait anxiety: social evaluation, physical danger, daily routines and other-undetermined (e.g., self-disclosure, separation anxiety).

Anxiety is not to be confused with stress (Anxiety and Depression Association of America, 2016b). Stress is a response to a threat or situation (Groberman, 2012). Anxiety is a reaction to the stress. For a diagnosis of anxiety symptoms must persist for 6 months. This duration period prevents stress from being mistaken as anxiety. Stress typically disappears as the stressor(s) disappear, while anxiety with no identifiable root cause, tends to be more long term and also more difficult to treat (Groberman, 2012).

3.7.2 ANXIETY AND PATIENTS WITH HCV

While most studies have concentrated on depression in patients infected with HCV infection, anxiety symptoms are also common. However, few controlled studies have evaluated the level and pattern of anxiety during treatment and post treatment. A 2001 study of 77 patients with HCV and using the HADS measure, found that both anxiety and depression were increased in HCV patients compared with controls (Goulding, 2001). The study found that participants in the HCV group were more than twice as likely as controls to score significantly higher anxiety levels. This study also reported that anxiety caused by chronic infection could lead to avoidance behaviour, inactivity, sleep and mood disturbances, tense muscles, and decreased exercise tolerance.

Erim and colleagues (2010) reported there was a high prevalence of anxiety and depression in HCV patients. This study of 81 HCV outpatients used the HADS to measure anxiety and depression. It was found that the mean value for anxiety ($M = 7.17; SD = 4.00$)
was significantly higher than in a healthy sample. Similar findings of higher anxiety in HCV patients were reported in an earlier study which found that, in addition to depression, anxiety symptoms were common in HCV patients. (Zignego et al., 2007). Using the STAI measure, Zignego and colleagues (2007) found that both state and trait anxiety were higher in HCV patients compared to a control group. Another study conducted in 2005, involving 90 HCV patients found anxiety was not associated with the adverse experiences of HCV illness (Golden et al., 2005). In this study it was specifically found that although depression was associated with a number of risk factors such as higher illness stigma, poor social adjustment and higher levels of subjective physical symptoms, anxiety disorders were not associated with any risk factors. These findings were supported in a subsequent 2007 study which reported an association between HCV and depression independent of treatment with interferon-alpha but by contrast found no association between HCV and anxiety (Carta et al., 2007). A more recent study by Carta and colleagues (2012) showed that depression and anxiety have been reported in about one third of HCV patients.

3.7.3 **ANXIETY AND RELATIONSHIP WITH OTHER PSYCHOLOGICAL SYMPTOMS AND GENDER**

There have been several studies involving anxiety and chronic illnesses which are worthy of consideration for this review. A study involving primary biliary cirrhosis (PBC) and which used the HADS to measure anxiety and depression, found patients who reported higher levels of fatigue were significantly more anxious, more depressed and were more likely to worry (Blackburn, Freeston, Baker, Jones, & Newton, 2007). The researchers reported that patients were adamant that lower mood and higher levels of worry were a consequence of fatigue rather than vice versa.

A study of 230 thyroid cancer patients found that depression correlated highly with anxiety ($r = .63, p < .01$) (Tagay et al., 2007). This study found that social support and sense
of coherence were negatively correlated with anxiety meaning that low social support and low sense of coherence increased the vulnerability to anxiety. Subsequently, a 2009 study of coronary artery disease reported that the most important predictor of depression was the stable personality trait of neuroticism followed by beliefs about consequences (Stafford, Berk, & Jackson, 2009). This study used the self-report version of the Revised NEO Personal Inventory (NEO PI–R) and the International Personality Item Pool Representation of the NEO PI-R (IPIP-NEO). Limitations of this study were sample bias, with respondents being more likely to be male and on average younger than non-respondents. There was also a possibility that patients with depression were less likely to participate in the study.

3.7.4 ANXIETY POST HCV TREATMENT

Ongoing anxiety post HCV treatment has been reported by both patients who achieved SVR and non-responders. Ware and colleagues (1999) found patients reported significant anxiety symptoms post PEG IFN + RBV therapy. Of those patients who achieved SVR, 50% of patients reported anxiety at baseline and 24% of patients reported anxiety at 24 weeks post treatment end ($p < .001$). Of those patients who were non-responders 52% reported anxiety at baseline and 45% reported anxiety 24 weeks post treatment end ($p < .01$).

The Hepatitis C Trust (2007) web-based survey of 500 respondents who had undergone PEG IFN + RBV therapy reported anxiety in 56% of the participants within the first 6 months of treatment follow-up. Furthermore, 45% of participants reported fatigue from 6 months to 12 months of treatment follow-up and 32% of participants reported fatigue after 12 months or longer post treatment. According to the Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-V) fatigue is a symptom of generalised anxiety disorder (GAD) (American Psychiatric Association, 2013).

The Hopwood (2009) qualitative study of PEG IFN + RBV patients showed that one of the 27 participants specifically reported that anxiety was a post treatment symptom. Also 8
of the participants reported cognitive effect which included anxiety in the definition. The Hopwood (2009) study reported that for some patients achieving SVR meant relief from worrying about future health consequences of HCV. However, some patients reported having difficulty noticing any improvement in health, while others perceived new health problems. Those patients who were non-responders reframed treatment failure. Reframing was assisted by factors like improved liver function tests and the prospect of more effective treatments becoming available in the near future. Some patients reported they were still concerned that HCV may have caused damage which may compromise their future health. Furthermore, because of the lack of information from specialists, some patients referred to internet anecdotal evidence about serious ongoing treatment-related side effects. Referring to the internet and reading about negative treatment and outcome experiences from other persons infected with HCV was reported as provoking anxiety in many patients, both those who achieved SVR and non-responders.

3.7.5 SUMMARY

Most HCV research has concentrated on depression rather than anxiety. Results of research into HCV and anxiety have shown conflicting results with some studies showing a relationship between HCV and anxiety (Constant et al., 2005a; Erim et al., 2010; Goulding, 2001; Zignego et al., 2007) while others have shown no relationship (Carta et al., 2007; Golden et al., 2005). Ongoing anxiety post treatment has been reported by both patients who achieved SVR and non-responders.

3.8 COGNITIVE FUNCTIONING AND HCV

3.8.1 COGNITIVE FUNCTIONING AND PATIENTS WITH HCV

Because of the involvement of other factors which are concomitant with the liver disease HCV is considered to be a systemic disease (Adinolfi et al., 2015). Studies have shown evidence of cognitive problems with HCV patients (Hilsabeck, Hassanein, Carlson,
Ziegler, & Perry, 2003) and neuropsychological symptoms and hepatic encephalopathy are common among HCV patients (Forton, Taylor-Robertson, & Thomas, 2006; Solinas et al., 2015). Indeed up to 50% of chronic HCV patients have reported neuropsychiatric disorders including cognitive impairment (Monaco et al., 2012; Origgi, Vanoli, Carbone, Grasso, & Scorza, 1998). However, it is unclear whether neurological symptoms are a function of liver disease, peripheral inflammation or direct infection of the CNS (Fletcher & McKeating, 2012). Also the extent to which HCV may cause irreversible neurodegenerative brain damage is unclear (Solinas et al., 2015).

Studies have also shown that cognitive impairment may occur early on the onset of HCV infection and prior to cirrhosis and that HCV infection itself may affect cognitive functioning (Forton et al., 2006). Furthermore, many HCV patients report having attention problems and deficits in concentration and memory (Forton et al., 2006). When evaluated with suitable neuropsychological measures the majority of HCV patients show alterations of verbal learning, attention, executive function and memory (Forton et al., 2003; Kramer et al., 2002; Kramer et al., 2005).

Using depression, fatigue and QOL measures, computer-based assessment, and cerebral proton magnetic resonance spectroscopy, Forton and colleagues (2002) found that cognitive impairment was not attributed to depression, or fatigue, or prior use of intravenous drugs. The study found a significant decrement in concentration and memory speed in HCV-infected patients compared to healthy controls. Fontana and colleagues (2005) using similar measures as used in the 2002 study investigated 201 HCV patients in the Hepatitis C Long-term Treatment against Cirrhosis (HALT-C) trial. In that study, it was found 33% of participants showed mild cognitive impairment particularly in verbal recall and working memory domains.
Weissenborn and colleagues (2004) compared the psychometric results of 30 HCV-infected patients who had mild liver disease to a healthy control group. That study found significant attention deficits in the HCV-infected patients compared to controls and moderately fatigued HCV-infected patients were more compromised than the mildly fatigued HCV-infected patients. A subsequent study by Weissenborn and colleagues (2009) reported psychometric tests showed deficits in attention and verbal learning ability for patients infected with HCV.

The Hannover and Liepzig qualitative studies (Tillman et al., 2011) showed that there was greater mental impairment in patients with HCV compared to other liver diseases. However, Spiegel and colleagues (2005) found, when HCV patients were compared to a control group, the impact of HCV was most dramatic in SF-36 domains: Social Functioning (SF), Physical Functioning (PF), General Health (GH) and Vitality (VT). It has been shown that HCV-infected patients are severely impaired in their Mental Health (MH) compared to their Physical Health (PH), in contrast to most chronic diseases where mental impairment is less evident than physical impairment (Foster, 2009). However, while another study did show a strong relationship between HCV infection and impaired physical health (Ashrafi et al., 2012), it has also been shown that in patients with HCV (but not HBV) there was an inverse correlation between levels of brain-derived neurotrophic factor and physical health (Modabbernia et al., 2011).

Cordoba and colleagues (2003) results were in contrast to the majority of other research findings. Their study found that HCV-infected patient’s neurocognitive results were no different from those of healthy controls and only patients with decompensated cirrhosis showed worse results. Impairment was reported in attention, executive functioning, and motor performance. No reasons have been put forward for this finding which contradicted the majority of research findings. There were however a low percentage of ex-injecting drug
users and the study excluded patients with current symptomatic medical comorbidities. A further study reported slight attention deficits and impairment in their study of 37 patients with chronic HCV infection compared to 46 healthy controls. The researchers concluded that the cognitive dysfunction in the HCV-infected patients showed little clinical significance (McAndrews et al., 2005).

3.8.2 COGNITIVE FUNCTIONING AND RELATIONSHIP WITH OTHER PSYCHOLOGICAL SYMPTOMS

A number of studies have investigated the relationship between common symptoms experienced by HCV patients and cognitive impairment. While cognitive impairment is well documented in HCV patients, its effect on HRQL is not clearly known (Forton et al., 2006). Glacken and colleagues (2003) reported that forgetfulness and lack of concentration appeared the most universal aspects of the cognitive dimension of fatigue. In their qualitative study, they reported that one participant stated that the cognitive dimension of fatigue was “like a few notches have been chopped off your IQ”. Cognitive impairment in HCV patients can also be related to sleep disorders. Studies have shown that sleep disturbance impairs cognitive function (Bonnett & Rosa, 1987). It has also been reported that cognitive functioning may impair HRQL (Strauss et al., 2014; Younossi et al., 2007).

3.8.3 COGNITIVE FUNCTIONING AND HCV TREATMENT

A decline in cognitive functioning for HCV patients, resulting from antiviral therapy with interferon, has been reported in a number of studies (Kraus, Schafer, Wisligmann, Reimer, & Scheurlen, 2005; Reichenberg, Goerman, & Dieterich, 2005; Wobrock et al., 2009). However, less attention has been given to investigating whether cognitive impairment can be reversed after IFN therapy. Fontana and colleagues (2007) investigated HCV patients who were prior non-responders who were retreated with PEG IFN + RBV for 24 weeks \((N=177)\) or 48 weeks \((N=57)\). At weeks 0, 24, 48 and 72, patients were assessed using 10
standardized neuropsychological tests. The patients who completed 48 weeks of treatment reported significant increases in difficulty in concentrating, verbal recall and working memory, but improved after treatment cessation. The study also found that cognitive impairment did not increase during the first 24 weeks for both the 177 patients with 24 weeks’ therapy (34% versus 32%, $p = 0.64$) and the 57 patients with 48 weeks of therapy ($p = 0.64$). The researchers concluded with the suggestion “that self-reported symptoms of impaired cognition were more likely related to the systemic and psychiatric side effects of antiviral treatment rather than measurable changes in cognition” (Fontana et al., 2007, p.1154). In cognitive assessment the Fontana and colleagues (2007) study used Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1939), Visuometer, Wisconsin Card Sorting Inventory (WCSI), and for verbal processing the Controlled Oral Word Association Test (COWA).

A study of 34 patients by Thein and colleagues (2007) investigated the hypothesis that HCV therapy with PEG IFN + RBV improves cognitive performance independent of effects on mood and HRQL. The 34 participants included 19 HCV mono-infected and 15 HCV/HIV co-infected individuals who completed neuropsychological and HRQL assessments at baseline, at 18 weeks and 42 weeks (for the 48-week treatment group) after starting treatment and at 24 weeks following treatment end date. The cognitive assessments used were: National Adult Reading Test (NART) (Nelson & Willison, 1991), Trail Making Tests (TMT) Part A and Part B (Reitan, 1958), and the computer-based performance test, CogState (Cysique, Maruff, Dorby, & Brew, 2006). The study reported there were no significant effects of PEG IFN + RBV on cognitive functioning in the HCV-mono-infected group. Other findings of the study were that SVR was associated with improvement in some measures of cognitive functioning and that the decrease in reaction time during PEG IFN +
RBV therapy was reversible after cessation of therapy except for a single task relating to the speed of simple identification.

Meguid and Moussa (2010) investigated two groups of 30 HCV patients. One group (Group A) were treated with PEG IFN + RBV (10 patients dropped out and 20 were treated for 24 weeks). Group B did not commence treatment due to lack of funding. At week 24 of therapy patient’s cognitive abilities were assessed using the WAIS, Wechsler Memory Scale-Revised (WMS-R) and the Benton Visual Retention Test (BVRT). When Group A were compared to Group B after 24 weeks of therapy, Group A scored significantly less on mean, performance, and verbal IQs \((p = 0.017)\) and total scores \((p = 0.005)\) respectively. Significant differences were found in perception and long-term memory \((p = 0.001)\), Visuo-motor coordination \((p = 0.037)\) and abstract thinking \((p = 0.013)\). There was no significant difference in sustained attention between the two groups. The study did not show baseline scores or follow-up scores at any time after therapy was completed.

3.8.4 **COGNITIVE FUNCTIONING POST HCV TREATMENT**

Forton and colleagues (2002) found that concentration and memory speed were significantly decreased in HCV-infected patients compared to healthy controls, but patients who achieved SVR showed cognitive performance equal to controls. Kraus and colleagues (2005) found that IFN had a negative impact on vigilance, attention and working memory in a 3-8-month full dose IFN-base treatment. The study also found that cognitive functioning returned to baseline 6 weeks after the end of treatment. The study was not designed to evaluate the effect of SVR.

Kraus and colleagues (2013) investigated 168 with chronic HCV infection, 116 of whom achieved SVR after undergoing treatment with PEG IFN + RBV. The study used the Test for Attentional Performance (TAP). When tested at least 12 months after the termination of their treatment, those patients with SVR had improved significantly compared to their pre-
treatment performance in three of five TAP subtasks (vigilance, shared attention: optical task and working memory). Those patients who did attain SVR showed no significant long-term changes in neurocognitive performance in all five TAP subtasks. Solis-Munoz and colleagues (2014) highlighted limitations to the findings of the Kraus and colleagues (2013) study. They refer to the study not being blinded and therefore if the patients who attained SVR were informed of their favourable progress then this may have affected test results. Also they noted that no information was provided about the confounding factor of depression or medication, adding that depressed patients may not perform as well as patients who were not reporting depression (Solis-Munoz, Mingote-Adan, & Solis-Herruzo, 2014).

The Hepatitis C Trust (2007) web-based survey of 500 respondents who had undergone PEG IFN + RBV therapy reported “brain fog” as a significant side effect in 61% of the participants within the first 6 month of treatment end follow-up. Furthermore, 47% of participants reported “brain fog” from 6 months to 12 months of treatment end follow-up and 35% continued to report “brain fog” 12 months or longer after treatment end. In addition, The Hopwood (2009) qualitative study of PEG IFN + RBV patients reported that 8 of the 27 study participants reported cognitive effects after treatment end. Four of those eight had achieved SVR. Furthermore, one of the 27 study participants reported “brain fog” after treatment end. That one participant had achieved SVR after PEG IFN + RBV therapy.

Cognitive psychiatric symptoms effects in the study were described as:

“like depression as well as cognitive deficits like poor memory, poor concentration, inability to speak clearly and/or speak properly and the inability to write/read at participant’s pre-treatment levels” (Hopwood, 2009, p.24).
3.8.5 SUMMARY

Cognitive impairment is reported in more than 50% of HCV patients and there are reports of greater mental impairment in HCV patients compared to other liver diseases. Studies have shown that cognitive impairment is mainly in attention, verbal learning, concentration, executive functioning, and memory. Studies have also shown that cognitive impairment may occur early in the onset of HCV infection and prior to cirrhosis and that HCV infection itself may affect cognitive functioning. However, it is unclear whether neurological symptoms are a function of liver disease, peripheral inflammation, or direct infection of the CNS. It has been suggested that self-reported symptoms of impaired cognition were more likely to be related to the systemic and psychiatric side effects of treatment rather than measurable changes in cognitive functioning. Furthermore, it has been reported that patients attaining SVR may have improved cognitive functioning compared to pre-treatment. However, a number of confounding factors may affect this finding. Finally, some studies have observed that 12-month post treatment end, those patients with SVR improved significantly compared to their pre-treatment performance.

3.9 PATIENT SATISFACTION AND HCV

3.9.1 PATIENT SATISFACTION AND PATIENTS WITH HCV

There is limited published data on patient satisfaction in relation to HCV patients and treatment. Any measure of patient satisfaction may be specific to the hospital treating the patient but it is of benefit to investigate whether patient satisfaction, in general, has any relation with other factors such as QOL/HRQL, depression, anxiety and fatigue (Bair et al., 2007; Kleeberg et al., 2005).

A Canadian study by Balfour and colleagues (2004) investigated 111 consecutive consenting HCV patients at their first and 10-month follow-up HCV clinic visits. Their study found that at the initial HCV clinic visit 51% of patients reported their knowledge of HCV
was inadequate (i.e., “fair” or “poor”). In relation to satisfaction with HCV health care prior to the initial HCV clinic visit 51% reported the overall quality of health care as “good” or “excellent”, however 41% rated the quality of care as “fair” or “poor”. A substantial number (69%) of patients did not feel encouraged to be involved in making informed decisions concerning their health care prior to attending the clinic. Also 31% of patients were “dissatisfied” or “very dissatisfied” at not being able to access specialised multidisciplinary services such as pharmacies, psychologists, and social workers. At 10-month follow-up to the initial HCV clinic visit, 63 patients completed the follow-up questionnaire. There was no difference in baseline or follow-up satisfaction scores between patients who initiated interferon-based HCV drug therapy and those who did not. Also, at 10-month follow-up, a greater proportion of patients felt satisfied with their level of care. Furthermore, a greater proportion felt more actively involved in their treatment, reported their health care needs were more likely to be met, felt better able to cope with their illness, reported a better sense of satisfaction with their health care, and reported better satisfaction with their access to specialised multi-disciplinary services. The researchers concluded that:

“medical care alone is not enough to meet the needs of a patient population who require educational and psychosocial support to cope with a long-term and potentially life-threatening chronic illness” (Balfour et al., 2004, p.276).

Balfour and colleagues (2004) also added that there was a need to develop comprehensive multi-disciplinary HCV teams and advocated for a biopsychosocial model of health for HCV patients similar to that established for HIV care in Canada.

A study by Larney and colleagues (2014) found several factors involved in patient satisfaction affected treatment adherence. Patient adherence to treatment may be affected by:

- poor baseline knowledge of the disease and its transmission (Larrey et al., 2011a),
- poor knowledge of the factors that aggravate HCV infection (Larrey, 2002; Larrey et al., 2011a;
McHutchison et al., 2002; Ramesh & Sanyal, 2004; Russell et al., 2012; Weiss, Brau, Stivala, Swan, & Fishbein, 2009; Zanini et al., 2013; Zeremski et al., 2013), poor knowledge of the antiviral treatment (Burger et al., 2013; Evon et al., 2013; Larrey et al., 2011a; Weiss, Alcorn, Rabkin, & Dieterich, 2012; Weiss et al., 2009) and difficulties in taking the treatment (particularly in the case of triple therapy) (Bacon et al., 2011; Jacobson et al., 2011; Poordad et al., 2011; Zeuzem et al., 2011).

3.9.2 PATIENT SATISFACTION AND HCV TREATMENT

Better patient satisfaction may result in better treatment adherence. A study of PEG IFN + RBV patients revealed that therapeutic education by a specialised nurse increased the adherence to therapy (Larrey et al., 2011a). Patient adherence to HCV therapy may be difficult, Patients on triple therapy with boceprevir take one pill three times a day, along with twice-daily RBV pills and weekly PEG IFN injections. Maintaining this routine for 24 or 48 weeks can lead to “pill fatigue” or a lapse in medication adherence. A study of PEG IFN + RBV therapy (Re et al., 2011) showed that as treatment progressed, patients tended to miss doses of RBV. The study also showed a correlation between contentment and compliance. Patients whose side effects were addressed by medical personnel and were properly managed, felt better, and were more likely to adhere to treatment. The researchers noted that the findings were applicable to boceprevir-based triple therapy.

3.9.3 PATIENT SATISFACTION POST HCV TREATMENT

There is little research on post treatment outcomes that are related to patient satisfaction for HCV treatments. The Australian Hopwood (2009) qualitative study is a comprehensive study of patient satisfaction post HCV treatment. The study has highlighted several problems experienced by HCV patients and reported that little or no information was provided by specialists about what patients could expect in the month after treatment end, and what to do and where to go if they experienced health problems. While acknowledging that
generally, participants in the study had a great deal of admiration and gratitude for the work of the clinicians, there was no evidence of a systematic, patient-oriented procedure at the end of treatment where patients could access information and advice.

The Hopwood (2009) study included the responses of 27 patients who had undergone PEG IFN + RBV. Of the 27 patients 12 had achieved SVR, 13 had not, and 2 did not know their response outcome. The study highlighted several shortcomings in the follow up of care for HCV patients following treatment end. Patients reported that specialists usually trivialised or dismissed their testimonies of ongoing side effects from treatment. Patients said they were told that the level of drugs reduced quickly after treatment ceased. However, patients commented that specialists rejected the association between treatment and participant’s accounts of persistent side effects and symptoms, while patients perceived a direct causal link between treatment and ongoing symptoms.

Apart from a reminder to come back for their PCR test, patients in the Hopwood (2009) study said they were not given any information regarding counselling or assistance with ongoing health problems. Patients reported feeling intimidated by the clinic and the study showed that end of treatment information and advice was only available to those who had the opportunity to make an inquiry or who were confident enough to ask for it. Furthermore, adjustment to life after treatment was compromised by clinics non-existence or inadequate treatment termination procedures. Several patients sought assistance from their GPs. However, patients reported that their GP did not know much about HCV treatments. Many patients turned to the internet as an alternative source of information. Some web postings from former patients presented anecdotal evidence about serious ongoing treatment-related side effects. These postings provoked further anxiety in patients. Finally, it was felt that the lack of clinical research into post treatment health problems among patient’s
treatment for HCV and their specialist’s disengagement with these issues was feeding online
rumours and hysteria.

3.9.4 SUMMARY

Patient’s satisfaction is an important variable in treatment. It not only affects the
patients QOL and HRQL, and level of depression and anxiety, but also has an impact on
patient satisfaction and adherence to treatment. A review of literature indicates no
quantitative research has been undertaken relating to patient satisfaction and PEG IFN +
RBV therapy or triple therapy either during therapy, at treatment end or post treatment. The
little qualitative research that has been conducted with HCV shows participant’s satisfaction
and motivation, and the physician’s treatment experience, may be important for better
adherence to combination therapy for patients with chronic HCV. These factors validate
Balfour and colleagues (2004) conclusions that a comprehensive multi-disciplinary approach
is required in the treatment of HCV.

3.10 SUMMARY OF PSYCHOLOGICAL SYMPTOMS AND HCV,
PEGYLATED INTERFERON PLUS RIBAVIRIN THERAPY AND
TRIPLE THERAPY

A consideration of psychological symptoms relating to patients infected with HCV,
and HCV therapy at baseline, treatment end and three-month follow, from a health
psychology perspective, is important. Research to date has shown that certain psychological
symptoms may have an impact on HCV treatment adherence, treatment contra-indication,
SVR and a patient’s overall prognosis. Varying degrees of research to date have investigated
the relationship between the psychological symptoms of QOL and HRQL, fatigue, sleep
disorders, mood states disturbance, depression, anxiety, cognitive function, and patient
treatment dissatisfaction and HCV infection, and HCV therapy with PEG IFN + RBV therapy or triple therapy.

A review of the literature indicates that most investigations involving PEG IFN + RBV therapy have concentrated on depression and HRQL and have been cross sectional. Furthermore, the little research on post treatment outcomes has produced differing results.

There are major gaps in current research on the relationship between other psychological symptoms despite there being evidence from research and anecdotally these other effects may also influence HCV treatment compliance, treatment discontinuation, treatment contra-indication, SVR and a patient’s overall prognosis.

A review of the literature indicates that no research has been conducted on the relationship between the psychological symptoms of QOL, fatigue and sleep disorders, mood states disturbance, depression, anxiety, cognitive dysfunction, and patient dissatisfaction.

The review of the literature also identifies similar gaps in research involving triple therapy, but even more so. The fact that more research has been conducted with PEG IFN + RBV than triple therapy may be because PEG IFN + RBV has been available for a longer time. Finally, there is a paucity of New Zealand (NZ) research relating to HCV, and HCV therapy and triple therapy outcomes in the NZ population.

The measurement of successful HCV therapy should not only consider physiological outcomes, such as SVR, but must also include psychological outcomes. Additional data from the present study is desirable in order to further assess and improve patient adherence, treatment outcomes and patients QOL, for patients undergoing both PEG IFN + RBV therapy and triple therapy. The proposed framework presented in Chapter Four, along with the empirical evidence discussed in this chapter form the rationale, aims, objectives, and hypotheses of the present study.
CHAPTER FOUR
RATIONALE, AIMS, OBJECTIVES AND HYPOTHESES

4.0     RATIONALE

The success of any HCV therapy should not only be measured by physiological outcomes, but must also include the measurement of psychological outcomes. Therefore, research which investigates effects that comprise psychological health during and post HCV therapy is warranted.

A review of the literature and anecdotal evidence obtained from patients and clinicians involved with PEG IFN + RBV and triple therapy suggests that QOL and HRQL, fatigue, sleep disorders, mood states disturbance, depression, anxiety, cognitive dysfunction, and patient satisfaction may, to varying degrees, be affected by these treatments. The overall aim of the proposed study is to examine the relationship between these psychological symptoms and HCV-infected patients treated with PEG IFN + RBV therapy or triple therapy at the three time points: baseline, at therapy end and three-month follow-up post treatment.

To date, much of the research which has investigated psychological outcomes in patients with HCV infection has concentrated on relationships between a patient’s HRQL, depression, treatment adherence and SVR. Much of that research has related to the PEG IFN + RBV therapy. There has been little research on the relationship between triple therapy and QOL/HRQL and depression. Furthermore, there has been a paucity of studies which have investigated fatigue and sleep disorders in both therapies, particularly when it comes to post treatment. Finally, most of triple therapy research has concentrated on the physical side effects, although a few studies have indicated that depression and fatigue as psychological symptoms contribute to treatment non-adherence.
Fatigue, sleep disorders and anxiety have all been shown to be related to depression and to a decrement in QOL and HRQL. Also, studies of patients with chronic illness have shown anxiety to be highly correlated to depression. Studies have also found that individuals who reported high fatigue levels, a symptom reported by many HCV sufferers, were significantly more likely to be more depressed, more anxious, and more likely to worry. However, a review of data suggests there are few research studies on the relationship between fatigue, sleep disorders and anxiety, and depression in HCV patients presenting for HCV therapy, during therapy and post therapy. In addition, there is little research in patients presenting for HCV therapy, during and post therapy and mood state disturbance, cognitive dysfunction, and patient treatment satisfaction. Furthermore, a review of literature reveals a gap in research investigating the effect of psychological symptoms, and gender on PEG IFN + RBV therapy and triple therapy adherence and SVR. In particular, there is a paucity of NZ research in these psychological symptoms.

It is reported that one of the main reasons for discontinuing HCV therapy is a decrement in QOL or HRQL. However, little research has investigated which psychological symptoms are associated with QOL or HRQL outcomes. The psychological symptoms QOL and HRQL, fatigue, sleep disorders, depression, anxiety, mood states disturbance, depression, anxiety, cognitive dysfunction, and treatment satisfaction may all have a varying degree of impact on HCV treatment adherence and outcomes, therefore it is beneficial to include those symptoms in ongoing HCV research and in any intervention that may increase the success of HCV therapy. The proposed study is also relevant because of the substantial financial cost of the drugs used in the treatment (see Appendix G). In addition to the cost of the drugs, there are the added delivery costs such as doctors’ and nurses’ time and hospital overhead expenses. Because of the high cost of treatment, both the monitoring of the cost-effectiveness of treatment and ensuring the success of treatment are critical.
The proposed research is a prospective cohort study investigating the relationship between HCV infection, PEG IFN+ RBV therapy and triple therapy and the psychological symptoms of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, cognitive function, and patient treatment satisfaction, at the three time points: baseline, treatment end and three-month follow-up to treatment end.

Finally, a health psychology perspective has been used in the proposed study. An early definition of health psychology by Matarazzo (1982) is still commonly quoted. Maratarazzo (1982, pg. 4) defined health psychology as “the aggregate of the specific educational, scientific, and professional contributions of the discipline of psychology to the promotion and maintenance of health, the prevention and treatment of illness, and the identification of etiologic and diagnostic correlates of health, illness, and related dysfunction and to the analysis and improvement of the health care system and health policy formation”.

More recently Ogden (2012) stated health psychology is concerned with the relationship between psychological, behavioural and social factors and physiological health and illness. Health psychology takes a biopsychological approach, recognising that health is a product not only of physiological processes, but also of psychological, behavioural and social processes (Ogden, 2012). The understanding of psychological, behavioural and social factors that influence physiological health and the application of that knowledge may enable the improvement of both physiological and psychological health of an individual (Matarazzo, 1982).

4.1 AIM, OBJECTIVES, AND HYPOTHESES

4.1.1 AIM

The aim of the proposed study is to describe the psychological symptoms of patients with HCV infection who are presenting (baseline) for PEG IFN + RBV and triple therapy,
and to investigate whether symptoms worsen or improve at end of treatment compared to baseline and whether patients report further change at three-month post treatment follow-up.

4.1.2 OBJECTIVES AND HYPOTHESES

The objectives and hypotheses of the two treatments for HCV; Study 1, PEG IFN + RBV and Study 2, triple therapy are:

Objective 1:

To determine whether the psychological symptoms at baseline are comparable to the norm referenced clinical populations of the standardized measures of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, and cognitive function.

Hypothesis 1:

The psychological symptoms reported by patients presenting for PEG IFN + RBV therapy and triple therapy will be poorer than other norm referenced clinical populations of the standardized measures of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, and cognitive function.

Objective 2:

To describe the sociodemographic characteristics and psychological outcomes of patients presenting for PEG IFN + RBV therapy and triple therapy at baseline (prior to receiving any treatment). Self-reported symptoms will be obtained from standardized measures of the following: QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, and cognitive function.

Hypothesis 2:

There will be no association between sociodemographic factors at baseline and the severity of symptoms reported by patients presenting for PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2).
Objective 3:

To describe QOL and investigate the correlation between QOL and psychological symptoms in patients presenting for PEG IFN + RBV therapy and triple therapy at baseline.

Hypothesis 3:

There will be a significant correlation between QOL, as a measure of satisfaction, and psychological symptoms including fatigue, sleep disorders, mood state disturbance, depression and anxiety, cognitive function, and patient satisfaction at baseline for PEG IFN + RBV therapy and triple therapy patients.

Objective 4:

To determine whether the self-reported symptoms of: QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function, and patient satisfaction in PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2) worsen at treatment end compared to baseline, but improve at three-month follow-up post-treatment in comparison to treatment end and baseline.

Hypothesis 4:

The psychological symptoms of QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function, and patient satisfaction will worsen from baseline to treatment end with PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2), but will improve at three-month follow-up post-treatment when compared to baseline and treatment end.

Objective 5:

To compare, at treatment end and at three-month follow-up after treatment end, the psychological outcomes of patients who received PEG IFN + RBV (Study 1) with those who received triple therapy (Study 2).
Hypothesis 5:

The impairment of psychological symptoms will be significantly greater for triple therapy patients than for PEG IFN + RBV therapy at end of treatment, but there will be no significant difference at three-month follow-up to treatment end.

Objective 6:

To investigate the number of participants in PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2) who completed therapy and who achieved SVR.

Hypothesis 6:

Compared to PEG IFN + RBV therapy (Study 1), triple therapy (Study 2) will have a higher percentage of participants who do not complete therapy, but will have a higher percentage of patients who achieve SVR for the participants who do complete therapy.

Objective 7:

To determine whether patients who achieve SVR after being treated with PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2) will report more improved psychological symptoms at three-month follow-up, compared to baseline, than non-responders.

Hypothesis 7:

Compared to non-responders, patients who achieve SVR after being treated with PEG IFN+RBV (Study 1) and triple therapy (Study 2) will report more improved psychological symptoms at three-month follow-up compared to pre-treatment (baseline).

Objective 8:

To determine whether the psychological outcomes for the participants who achieve SVR in PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2) differ to normative means.
Hypothesis 8:

In both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) at three-month follow-up to treatment end for patients achieving SVR, there will be an impairment of psychological symptoms compared to normative means.
CHAPTER FIVE

METHOD

5.0 STUDY DESIGN

The study reported in this thesis used a prospective longitudinal, repeated measures design to examine the psychological outcomes of two separate treatments for HCV (PEG IFN + RBV and boceprevir + PEG IFN + RBV (triple therapy)). All patients were evaluated at baseline, at treatment end and at three-month follow-up of treatment end. The accepted standard of care for the PEG IFN + RBV therapy is typically between 24 and 48 weeks. The accepted standard of care for triple therapy is typically 28 or 48 weeks, however treatment duration is assessed at 16 weeks and may vary depending on a patient’s condition, the side effects of the therapy and how well the patient is responding to treatment. Prior to beginning treatment (baseline) patients completed the Sociodemographic and background questionnaire that included gender, age, history of psychoactive drug use, whether they were receiving antidepressants, (see Appendix K). They also completed a psychological outcomes questionnaire that included the Quality of Life Inventory (QOLI), the Fatigue Severity Scale (FSS), the Pittsburgh Sleep Quality Inventory (PSQI), and the Profile of Moods States Questionnaire (POMS), the Hospital and Anxiety Depression Scale (HADS), the Addenbrooke’s Cognitive Examination (ACE-R), the Trail Making Tests (TMT A & B), and PSQ-18 Questionnaire (see Appendix K). At treatment end and 3-month follow-up patients completed the study questionnaire which comprised the QOL, FSS, PSQI, POMS, HADS, ACE-R, TMT (A & B) and PSQ-18 measures. The psychological outcomes questionnaire was administered again at treatment end (6-month post baseline for the PEG IFN + RBV therapy patients) and 12 months for the triple therapy patients and a further time at three-month post treatment end.
5.1 PARTICIPANTS

The study was granted ethics approval by the Ministry of Health Northern X Regional Ethics Committee on 17 May 2012 (reference NTX/12/04/029; Appendix K) and was approved until 31 December 2014. Recruitment commenced on May 18, 2012 and continued until 31 December, 2014. Separate ethics approvals were received from Auckland District Health Board (Auckland Hospital; 16 May 2012: Appendix L), and Waitemata District Health Board (North Shore Hospital; 27 March 2014; Appendix L).

Excluded from the present study were those individuals who were 18 years old or under, and non-English speaking patients. Also excluded were patients who were described under contraindications in section 4.3 of the Pegasys’ Summary of Product Characteristics (Roche, 2009b). Thirty patients infected with HCV who had been accepted for PEG IFN + RBV therapy, and 35 patients infected with HCV who had been accepted for triple therapy, by either Auckland or North Shore Hospitals, agreed to participate in the study after being approached by the research nurses at those two hospitals. Auckland and North Shore Hospitals are representative of other hospitals in New Zealand where patients are treated for HCV. The gastroenterology nurses for each hospital advised that all patients who had been accepted for these two therapies were asked to participate in this study.

The recruitment period was between May 18th, 2012 and December 31st, 2014. The 30 treatment naive patients in the PEG IFN + RBV (Study 1) included 19 males whose ages ranged from 35 years to 69 years ($M = 51.70, SD = 7.47$) and 11 females whose ages ranged from 37 years to 56 years ($M = 46.70, SD = 4.18$). The research nurses advised that three patients (two male and one female) commencing PEG IFN + RBV therapy declined to participate in the study stating they ‘could not be bothered’ and ‘did not have time’. The 35 treatment naive HCV patients in the triple therapy (Study 2) included 27 males whose ages ranged from 39 years to 67 years ($M = 53.30, SD = 8.42$) and 8 females whose ages ranged
from 48 years to 57 years ($M = 51.30$, $SD = 7.3$). The research nurses advised that three
patients (two males and one female) commencing triple therapy declined to participate in the
study stating they ‘could not be bothered’ and ‘did not have time’.

Twenty-six (86.7%) of participants in the PEG IFN + RBV (Study 1) were of New
Zealand Caucasian ethnicity. For the PEG IFN + RBV (Study 1), 26 patients (16 males and
10 females) completed the treatment end questionnaire and 25 patients (15 males and 10
females) completed the three-month follow-up questionnaire. Three males and one female
stopped the PEG IFN +RBV therapy treatment due to the side effects, while one male died
after treatment end. The death of the male patient was not attributable to the PEG IFN + RBV
treatment. For the triple therapy (Study 2), 27 participants (20 males and 7 females)
completed the treatment end and the three-month follow-up questionnaires. Seven males and
one female stopped the triple therapy treatment due to the side effects. Twenty-eight (80%) of
the participants were of New Zealand Caucasian ethnicity.

5.2 MEDICATION

5.2.1 PEG IFN +RBV THERAPY

Two forms of PEG IFN are available; peginterferon alpha-2a (40kDa) (Pegasys)
produced by Roche (NZ) Limited and peginterferon alpha-2b (12kDa) (Peg intron or
Pegatron) produced by Schering-Plough (NZ) Limited. The participants in the present PEG
IFN + RBV therapy study group were treated with Pegasys. During treatment each patient
was initially supplied with a combination pack which contained 4 Pegasys pre-filled syringes
and subcutaneous needles and one bottle of Copegus (containing either 168 or 112 tablets
depending on the criteria of the patient’s weight). Each pack contained enough medicine for 4
weeks of treatment. Pegasys was in liquid form supplied in a pre-filled syringe with a
stainless-steel needle. Pegasys was injected weekly by the patients themselves by
subcutaneous injection. Each injection contained 180mcg/0.5ml of Pegasys. All patients
received the same dosage of Pegasys. Patients were supplied a new combination drug pack
every four weeks.

The Copegus tablets are taken orally daily. Each Copegus tablet is 200mg and dosage
was dependent on the genotype and weight of the patient. HCV genotype 1 and 4 patients
with a weight under 75 kilograms were prescribed five 200 mg Copegus tablets daily and
were supplied with a bottle containing a monthly supply 168 tablets. HCV genotype 1 and 4
patients with a weight over 75 kilograms were prescribed six 200 mg Copegus tablets daily
and were also supplied with a bottle containing a monthly supply of 168 tablets. HCV
genotype 2 and 3 patients were prescribed 4 x 200 mg Copegus tablets daily and were
supplied with a bottle containing a month’s supply of 112 tablets (see Table 5.1). The
patient’s weight and genotype were the only criteria for dosage variance for Copegus. An
increase in the undetectability of serum HCV RNA or greater than 2 log reduction from
baseline HCV RNA in the first 12 weeks of treatment (EVR), and SVR rates have been
shown to be related to the weight of the patient (Bain et al., 2008). Body Mass Index (BMI)
and other weight measures were not taken into consideration in determining dosage.

Table 5.1: PEGASYS and COPEGUS Dosing Recommendations (PHARMAC, 2009)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PEGASYS Dose</th>
<th>COPEGUS Dose</th>
<th>TREATMENT PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes 1, 4</td>
<td>180 mcg</td>
<td>&lt;75 kg=1000mg</td>
<td>48 weeks</td>
</tr>
<tr>
<td></td>
<td>180 mcg</td>
<td>≥75 kg=1200mg</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Genotypes 2, 3</td>
<td>180 mcg</td>
<td>800mg</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>
5.2.2 **TRIPLE THERAPY**

Triple therapy (Study 2) patients were treated with boceprevir plus PEG IFN + RBV. Boceprevir comes as a capsule and is taken orally. It is usually taken with a meal or small snack three times daily (every 7 to 9 hours). Triple therapy treatment commences with a 4-week treatment of PEG IFN + RBV. The three medications (triple therapy) are then taken for 12 to 44 weeks. After this time the patient stops taking boceprevir but may continue to take PEG IFN + RBV for an additional number of weeks. The length of treatment for any patient depends on several factors such as the patient’s condition, whether there are side effects and how well the patient responds to the medication. For this study, all cirrhotic HCV patients received 48 weeks if they were responding to treatment. For treatment-naïve non-cirrhotic patients, all medication may have been stopped at 28 weeks if rapid virological response (RVR) was achieved, otherwise boceprevir is stopped and PEG IFN + RBV is continued for 6 months. For patients who were treatment experienced (previously responded but relapsed) triple therapy continues for 36 weeks (inclusive of initial 4 weeks of PEG IFN + RBV) if the patient achieved RVR, otherwise boceprevir is stopped and for 6 months the patient is treated with PEG IFN + RBV.

5.3 **MEASURES**

Baseline questionnaires used in the study measured the following (see Appendix K):

- Sociodemographic Questionnaire
- Quality of Life: Quality of Life Inventory  QOLI (Frisch, Cornell, Villanueva, & Retzlaff, 1992).
- Fatigue : Fatigue Severity Scale (FSS) (Krupp et al., 1989).
- Sleep : The Pittsburgh Sleep Quality Index  (PSQI) (Buysse et al., 1989).
• Depression: Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983).

• Anxiety Depression: Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

• Cognitive functioning: Addenbrooke’s Cognitive Examination Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006)

• Trail Making Tests: (TMT) (Corrigan & Hinkelday, 1987).

• Patient satisfaction: Patient Satisfaction Questionnaire Short Form (PSQ-18) (Marshall & Hays, 1994)

The measures are described in the following section.

5.3.1 SOCIODEMOGRAPHICS

The Baseline questionnaire included questions relating to sociodemographics including the patient’s date of birth, gender, family, highest educational qualification obtained, marital status, ethnicity, use of support services, anti-depressant drug usage history and psychoactive drug usage history.

5.3.2 QUALITY OF LIFE

The Quality of Life Inventory (QOLI) (Frisch et al., 1992) was used in the present study to measure quality of life (QOL). Most of studies to date relating to HCV have used the SF-36 measure which measures health related quality of life (HRQL). For the present study the QOLI was chosen because of the emphasis on life satisfaction, well-being, positive psychology, and positive mental health. Some of the areas of life measured by the QOLI are self-esteem, goals and values, work, family, community, love, and creativity which are all important to varying degrees for the ongoing mental health of the HCV patient after he or she has completed HCV treatment. These areas of life are also critical to the future wellbeing of
the individual who has lived with both the psychological and physiological adverse side
effects of being infected with HCV for many years.

Frisch (1994) states that the QOLI is a measure of life satisfaction, well-being,
positive psychology, and positive mental health. In a clinical setting, the QOLI is well suited
for planning, evaluating, and tracking medical and psychological treatment and patient
progress. Also, in research and quality assurance programs, QOLI test results can be used to
help measure treatment outcome for wide array of physical and psychological disorders. The
QOLI consists of 32 items in 16 areas of life including: health, self-esteem, goals and values,
money, work, play, learning, creativity, helping, love, friends, children, relatives, home,
neighbourhood, and community. In the first instance participants rate these areas in terms of
their importance to their overall happiness and satisfaction (0 = not important at all, 1 =
important, 2 = extremely important), and second in terms of their satisfaction with them on a
6-point scale ( -3 = very dissatisfied to 3 = satisfied). “The inventory’s scoring scheme
reflects the assumption that a person’s overall life satisfaction is a composite of the
satisfactions in particular areas of life weighted by their relative importance to the individual.
Thus, the product of the satisfaction and importance ratings for each area of life are computed
with weighted satisfaction ratings ranging from -6 to 6. Next, the overall life satisfaction, or
QOLI score, is obtained by averaging all weighted satisfaction ratings that have nonzero
importance ratings. This essentially allows items and areas to be omitted by individuals who
deem them irrelevant to their overall happiness or satisfaction, allowing for a subjective
measure that has both normative and ipsative features (Frisch et al., 1992, p.93-94). The test-
retest coefficients for the QOLI have been shown to range from .80 to .91. with Cronbach’s
alpha coefficients from .77 to.89 across 3 clinical and 3 nonclinical samples (Frisch et al.,
5.3.3 **FATIGUE**

Fatigue was measured using the Fatigue Severity Scale (FSS) (Krupp et al., 1989). This measure is designed to differentiate between fatigue from clinical depression since both shares a number of the same symptoms. The FSS has been used in a number of studies including research on fibromyalgia (Alexander et al., 1998), multiple sclerosis (MS), (Giovannoni, Thompson, Miller, & Thompson, 2001), Systemic Lupus Erythmatosis (SLE) (Austin, Maisiak, Macrina, & Heck, 1996) and cancer (Stone, Hardy, Huddart, Hern, & Richards, 2000).

The FSS has shown good psychometric qualities in research on HCV and is responsive to changes in sustained viral response (Bernstein et al., 2002). Furthermore, it has been reported that the FSS is a valid and reliable patient reported outcome tool appropriate for use in clinical trials with HCV-infected patients (Rosa et al., 2014).

The FSS comprises 9 statements concerning the respondent’s fatigue, e.g., how fatigue affects motivation, exercise, physical functioning, carrying out duties, interfering with work, and family or social life. Responses are measured using a 7-point Likert scale where 1 = Strongly Disagree and 7 = Strongly Agree. The score range is 1-7. The responses are summed and divided by the number of items for scale score. Higher scores indicate more severe fatigue. Healthy adults report a mean score of 2.30 ($SD = 0.70$). Respondents with depression alone (i.e. with no other reported illnesses or symptoms) score about 4.50 while respondents with fatigue related to MS, SLE and CFIDS average about 6.5 (Krupp et al., 1989). In a study of the validation of the measure, FSS scores were 3.00 ($SD = 1.08$) for healthy controls, 4.34 ($SD = 1.64$) in patients with sleep-wake disorders, and 4.66 ($SD = 1.64$) in MS patients. Among patients with sleep-wake disorders, the highest scores were found in patients with insomnia (4.78) and narcolepsy (4.75) (Valko, Bassetti, Bloch, Held, & Baumann, 2008).
The FSS shows good reliability with Cronbach’s Alpha of 0.89 for SLE subjects (N =28), 0.81 for MS subjects (N =25) and 0.88 for normal healthy adults (N =20). Test-retest with 2 points separated by 5-33 weeks showed no significant changes in FSS scores when no clinical change was expected (r = 0.84). The FSS has also been shown to be responsive to change. Clinical improvement after treatment was associated with a reduction in FSS score \( t(7) = 2.16; p = 0.01 \) (Krupp et al., 1989). A study of the validation of the FSS in chronic hepatitis C reported a difference of ≥ 0.7 in mean FSS scores can be considered a clinically important difference within groups over time or between groups. A one-point change is a conservative indicator of an important change in individual FSS scores (Rosa et al., 2014). Results of the Rosa and colleagues (2014) study suggest that an interpretable and meaningful improvement in fatigue occurs when there is an observed-group mean change in FSS total score of between 0.33 and 0.82.

The FSS differentiates between fatigue and depression which show several common symptoms. It also differentiates between various sleep-wake disorders and fatigue (Valko et al., 2008). A 2007 bibliography study of fatigue measurement scales reported at the time that the FSS was the most commonly used fatigue specific questionnaire (Hjollund, 2007).

5.3.4 SLEEP QUALITY

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to measure sleep quality. The PSQI differentiates good sleep from bad sleep and focuses on sleep quality and sleep patterns during the participant’s previous month. The PSQI covers the 7 equally weighted domains; subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction.

The PSQI questions 1 to 4 ask about specific information on such factors as: customary bed time and length of time to fall asleep. Questions 5 to 8 are answered on a scale of 0 to 3, with scale 0 indicating that no symptoms are present, while 3 on the scale indicates
the presence of the symptoms 3 or more times in the past week. Question 9 is answered on a 0 to 3 scale with 0 being “not a problem’ and 3 indicating “a very big problem”. Finally question 10 asks the patient to ask the patient’s bed partner questions about the patient’s behaviour while asleep (e.g. snoring, leg twitching).

Each question measures a specific area in which sleep dysfunction occurs. The 7 components assessed and their associated questions are:

- **Subjective sleep** Question 9 score
- **Sleep latency** Questions 2 (≤ 15 min =0, 16-30 min =1, 31-60 min =2, >60 min =3) + 5a score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)
- **Sleep Duration** Question 4 score (>7=0; 6-7 = 1; 5-6= 2, < 5 =3)
- **Habitual sleep efficiency** Questions 1, 3 and 4. (total hours asleep)/(total hours in bed)/(total hours in bed) x100. (If >85% =0, 75%-84% =1, 65%-74% =2, < 65% = 3)
- **Sleep disturbances** Sum of Questions 5b through 5j score (if sum is equal 0=0; 1-9=1; 10-18=2; 19-27=3)
- **Use of sleep medications** Question 6 score
- **Daytime dysfunction** Questions 7 score + 8 score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)

The global scores range from 0 to 21. All domain scores range from 0 to 3. A Global Score above 5 indicate clinically meaningful disturbed or poor sleep. Questions that request the evaluation of patient’s bed mate are not scored. The PSQI has been confirmed as a valid and reliable measure of sleep dysfunction in a range of populations including hepatitis C (De Almeida et al., 2011), psychiatric and sleep disorders(Buysse et al., 1989),somatic diseases
(Carpenter & Andrykowski, 1998), and cardiovascular disease and hospitalised older adults. Cronbach’s alpha coefficient produced an average internal consistency reliability estimate of .80 for the Global PSQI score across a number of patient populations with various physical disabilities (Carpenter & Andrykowski, 1998). The same study indicated that the PSQI is more highly correlated with sleep problems (range from $r = .65$ to $r = .77$) than with unrelated constructs such as the Profile of Mood States (POMS) total mood disturbance and depression (range from $r = .22$ to $r = .65$). Traditional norms for the PSQI are unavailable. The mean (SD) (study participant number) values are: mean score values for good sleeper controls 2.67 (SD = 1.70) (N = 52); Major depression controls 11.09 (SD = 4.31) (N = 34); Disorders of Initiating and Maintaining Sleep 10.38 (SD = 4.57) (N = 45) and Disorders of Excessive Daytime Somnolence 6.53 (SD = 2.98) (N = 17) (Buysse et al., 1989). The mean score for heterogeneous outpatient chronic pain is 11.57 (4.36) (N = 51) (Smith et al., 2000). The mean score for Primary Insomnia is 12.50 (SD = 3.80) (N = 80) (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). The PSQI has shown to have strong concurrent validity and can distinguish between people who have problems with sleep and those who do not. In the original study the cut-off of 5 correctly identified sleep quality in 88.5% of all patients. The Cronbach’s alpha for the PSQI has been shown to be 0.83 for its seven components (Buysse et al., 1989).

5.3.5 PROFILE OF MOOD STATES

The Profile of Mood States (POMS-2) (Heuchert & McNair, 2012) was used to measure transient, fluctuating feelings, and enduring affect state. This includes the assessment of affective traits, mood, and emotion. POMS-2 measures the following 6 scales: anger-hostility (AH), confusion-bewilderment (CB), depression-dejection (DD), fatigue-inertia (FI), tension-anxiety (TA) and vigour-activity (VA). In addition, there is a seventh scale Friendliness which has been determined to be too weak for valid scoring. Mood states,
unlike personality traits, are thought to be transitory and specific to a situation. Moods, however, can also be measured for recent prolonged periods such as the past several months.

The POMS-2 questionnaire consists of 65 adjectives (see Table 5.3) that describe moods or feelings of the participant rated on a 5-point Likert scale from “not at all” (0) to extremely (4). The range of scores (after excluding Friendliness scale with 7 adjectives) is 0 to 168, with a higher score indicating a greater total mood disturbance. Ratings are made in reference to how the respondent has been feeling during the past week, including the date of assessment. The Total Mood Disturbance (TMD) is assessed as \( AH + CB + DD + FI + TA - VA \). Since its publication the POMS-2 has been widely used particularly in drug evaluation and studies of psychotherapy change. The POMS-2 is internally consistent with a relatively stable factor structure. Cronbach’s alpha is reported to be between .82 and .96 (Lin, Hsiao, & Wang, 2014).

The POMS subscales for depression, anger and anxiety have shown significant positive correlations with other measures of the same construct. A more negative mood state (i.e. higher TMD score) was associated with higher levels of depression, anxiety, anger, feelings of fatigue and confusion, but with lower levels of vigour. The POMS shows excellent subscale consistency with Cronbach’s alpha coefficients reported of 0.90 for Depression, 0.89 for Anxiety, 0.87 for Fatigue, 0.86 for both Vigour and Anger and 0.84 for Confusion (Gibson, 1997). Gibson (1997) also reported that MANOVA showed significantly higher levels of TMD in a pain clinic group when compared to a healthy elderly group, \( F(7,47) = 10.05, p < .0001 \), thus highlighting the discriminative properties of the POMS measure in differentiating a group with known mood disturbances.
Table 5.2. Description of the POMS-2 scales (Heuchert & McNair, 2012)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger-hostility (AH)</td>
<td>A feeling of anguish and hostility -12 adjectives</td>
</tr>
<tr>
<td>Confusion-bewilderment (CB)</td>
<td>Reflects anxiety, bewilderment, and cognitive inefficiency-7 adjectives</td>
</tr>
<tr>
<td>Depression-dejection (DD)</td>
<td>Depression or self-inadequacy characterised by sadness, loneliness Guilt, worthlessness and hopelessness-15 adjectives</td>
</tr>
<tr>
<td>Fatigue-inertia (FI)</td>
<td>Reflects weariness, inertia, and low energy-7 adjectives</td>
</tr>
<tr>
<td>Tension-anxiety (TA)</td>
<td>Tension caused by anxiety and impatience-9 adjectives</td>
</tr>
<tr>
<td>Vigour-activity (VA)</td>
<td>Reflects cheerful mood-8 adjectives</td>
</tr>
<tr>
<td>Friendliness (F)</td>
<td>Positive factor reflecting interpersonal influences and mood-7 adjectives</td>
</tr>
</tbody>
</table>

TMD = Global indicator of emotional disturbance, psychological distress, or subjective wellbeing

5.3.6 DEPRESSION AND ANXIETY

Depression and anxiety were measured using the fourteen-item depression and anxiety subscales of HADS (Zigmond & Snaith, 1983) which scores the severity of the symptoms of anxiety and depression is a widely used measure for use in non-psychiatric medical patients. It does not include items such as fatigue and loss of appetite which may overlap with pain and medical symptoms. The HADS measure uses a fourteen-item format and the questions alternate between anxiety (seven items) and depression (seven items) with higher scores indicating higher levels of anxiety and depression. A four-point Likert-type scale is used to rate items and each response is assigned a score ranging from 0 to 3 so that total scores for both depression and anxiety range from 0 to 21. Generally scores between 0 and 7 are treated as normal, scores between 8 and 10 are treated as an indication of possible
clinical disorder and 11 plus scores are indicative of the probable presence of anxiety or depression (Zigmond & Snaith, 1983).

HADS has been confirmed as a valid and reliable measure of anxiety and depression in a range of populations with high mean internal consistency scores for both anxiety (Cronbach’s alpha =0.83) and depression (Cronbach’s alpha = 0.82) scales (Bjelland, Dahl, Haug, & Neckelman, 2002). The HADS scales have also shown good concurrent validity with a number of other measures of depression and anxiety. The scale has good face validity and it is easy to complete and acceptable to patients (Zigmond & Snaith, 1983). Also the construct validity of the HADS as a measure of two factors was shown in a study of 568 cancer patients which found that two independent variables accounted for 53% of the variance (Moorey et al., 1991). Finally the HADS measure has been used in research over a number of populations including diabetes (Nishimur et al, 2004), thyroid arthritis (Tagay et al., 2007) and fatigue in primary biliary cirrhosis (Blackburn et al., 2007).

5.3.7 COGNITIVE FUNCTIONING

The questionnaire included the Addenbrooke’s Cognitive Examination Revised (ACE-R) (Mioshi et al., 2006) and the Trail Making Test (TMT) (Corrigan & Hinkelday, 1987). The ACE-R is an update of the Addenbrooke’s Cognitive Examination (ACE) (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). The ACE-R assesses five sub-domain scores (orientation/attention (18 points), memory (26 points), verbal fluency (14 points), language (26 points) and visuo-spatial (16 points)). A total score is 100, composed by the addition of all the domains scores, with higher scores indicating better cognitive functioning. The reliability of the ACE-R has been reported as being very good with Cronbach’s alpha showing 0.80 (Mioshi et al., 2006). A total normative score of 96 ($SD = 2.70$) is based on a sample of 53 controls with mean age 68.7 ($SD = 7.00$) and mean education 14.1 years ($SD = 2.80$). The ACE-R cut-off score for dementia is 82/100.
The Trail Making Tests (TMTs) are measures of attention, speed, and mental flexibility. Part A requires the individual to draw lines to connect 25 encircled numbers distributed on a page and tests visual scanning, numeric sequencing, and visuomotor speed. In Part B individuals must alternate between numbers and letters and takes longer to complete than Part A. Part B tests cognitive demands including visual motor and visual spatial abilities and mental flexibility. Scoring is measured by the time taken to complete the task. The results for both Trails are reported as the number of seconds required to complete the task. Higher scores indicate greater cognitive impairment. Table 5.3 sets out the interpretation of TMT scores.

Table 5.3. Interpretation of Trail Making Tests (TMTs) Parts A and B scores

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Deficient</th>
<th>Rule of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part A</td>
<td>29 seconds</td>
<td>&gt; 78 seconds</td>
<td>Most in 90 seconds</td>
</tr>
<tr>
<td>Part B</td>
<td>75 seconds</td>
<td>&gt;273 seconds</td>
<td>Most in 3 minutes</td>
</tr>
</tbody>
</table>

There are some weaknesses in the TMT. Firstly, there is a test-retest error such that once an individual has taken the test, he/she is familiar with the test and therefore will take less time to complete it. This weakness is common in test-retest of measures of attention, speed, and mental flexibility. The test is also skewed towards more educated individuals and can be frustrating for individuals if they lose track of where they are and thus cannot proceed. However, this weakness was not thought to likely influence the results of the study as the study measured changes over time and was not measuring the difference in scores between participants. Normative score (in seconds) for the ages 45-54 are 31.58 ($SD = 9.93$) for Part A and 63.73 ($SD = 14.42$) for Part B (Tombaugh, 2004).
5.3.8  **PATIENT SATISFACTION**

The study used the Patient Satisfaction Questionnaire Short Form (PSQ-18) (Marshall & Hays, 1994) to measure patient satisfaction. The PSQ-18 consists of 18 items and is a short form of the Patient Satisfaction Questionnaire which consists of 80 items. However, the PSQ-18 retains many characteristics of the full-length version. The PSQ-18 has been confirmed as a valid and reliable measure with Cronbach’s alpha scores ranging from 0.82 to 0.88 (Marshall & Hays, 1994). The current study omitted two items (Item 7: I have to pay for more of my medical care than I can afford, and Item 9: Where I get medical care, people have to wait too long for emergency treatment) from the original PQ-Q-18 questionnaire presented to study participants as the items were not applicable to NZ HCV patients. This adjustment did not have any impact on the final patient satisfaction score.

The PSQ-18 yields separate scores for each of seven different subscales: General Satisfaction (items 3 and 15), Treatment Quality (items 2, 4, 6, and 12), Interpersonal Manner (Items 8 and 9), Communication (Items 1 and 11) and Financial Aspects (Item 5), Time Spent with Doctor (Items 10 and 13), and accessibility (Items 7, 14, and 16). The item references refer to the modified PSQ-18 items (refer Appendix M). The items are worded so that agreement reflects satisfaction with medical care, whereas other items are worded so that agreement reflects dissatisfaction with medical care. After item scoring, items within the same subscale are averaged to create the 7 subscale scores. The range for the total score is 16 to 80 with a higher score indicating more dissatisfaction with medical treatment. A score of 16 would indicate complete satisfaction with all aspects of treatment in the PSQ. The normative mean for the 16 questions in the PSQ-18 is 50.20 ($SD = 11.67$) (Marshall & Hays, 1994).
5.4 PROCEDURE

The research nurses in the Gastroenterology Department of each hospital were advised by the researcher of the study and of the inclusion and exclusion requirements. The research nurses agreed to recruit patients as patients attended their initial appointment for PEG IFN + RBV therapy or triple therapy treatment. At that time patients were to be given the first prescription for their medication.

The researcher was advised of each patient’s initial appointment by the research nurses. The researcher then attended the initial appointment but did not meet the patient until the patient had agreed to participate after their discussions with the research nurse. During the appointment the research nurse administered the HADS measure and completed a Pegylated Interferon/Standard Interferon Patient History Sheet. At the end of the appointment the research nurse asked the patient whether they would participate in the current study. Those who agreed to participate in the study were introduced to the researcher. Patients were then given a Participant Information Sheet (Appendix M) to read after which they were asked to sign the Consent Form (Appendix M). The patients then completed the self-report questionnaire which included; Sociodemographic section, and the QOLI, FSS, PSQI, POMS, ACE-R, TMT Parts A and B and the PSQ-18 measures. Following completion of the questionnaire the patients were thanked and advised that the researcher would communicate with them at treatment end and at three-month follow-up treatment end clinical appointments to complete the same questionnaire. The researcher was contacted when the patient’s treatment end and three-month treatment end follow-up clinical assessments were due. The patient’s completed the QOLI, FSS, PSQI, HADS, ACE-R, TMT Parts A & B, and the PSQ-18 measures at the treatment end and three-month follow-up supervised by the researcher. The baseline, treatment end and three-month follow-up questionnaires were completed by the participants at the hospital clinics, however some participants completed the three-month
treatment end follow-up questionnaires at the homes after the participant gave the researcher permission to do so. The researcher thanked the participant for their co-operation in the study. No participants in the study received any payment or compensation for participating in the study.

5.5 STATISTICAL POWER

A target sample size of 30-35 participants was set for each study which would give a moderate effect size ($d_z = .50$) for a repeated measures design where power was set at .80 with a two-tailed hypothesis and significance set at $p < .05$. However due to the drop out of participants from both studies and the death of one participant in the PEG IFN + RBV study only data from 25 participants in the PEG IFN + RBV study and 27 in the triple therapy study participants completed the three-month follow-up. Nonetheless, subsequent power analyses of data from recent longitudinal studies shows large effect sizes for differences between baseline and end of treatment scores on a number of psychological outcomes, including depression and fatigue (Huckans et al., 2015). Based on these analyses, a large effect size with a sample of 25 and 27 would provide adequate power to detect a difference between baseline and end of treatment follow-up at $p < .05$.

5.6 DATA ANALYSIS

The data were analysed using the computerised Statistical Package for the Social Sciences (SPSS, version 22.0). All tests were two tailed and $p < .05$ was considered statistically significant. Independent samples t-tests were used to examine differences between normally distributed continuous variables. Correlational analyses were conducted to explore the relationships between sociodemographic and psychological and variables. General linear model (GLM) repeated measures were used to determine whether there were
significant changes in psychological factors at the end of treatment and three-month follow-up for normally distributed continuous variables.

Before the $F$-ratio of the within-subjects effect (time) can be interpreted it must be ascertained whether the assumption of sphericity has not been violated (Coakes & Steed, 2007). Mauchley’s test of sphericity tests the hypothesis that the variances between conditions are equal (Field, 2005). If Mauchley’s assumption of sphericity is violated (i.e. $p < .05$) it is concluded that there are significant differences between the variances of differences (i.e. the condition of sphericity has not been met). If Mauchley’s test of sphericity is significant then several methods of correction are available to produce a valid $F$-ratio. In the current study if Mauchley’s assumption of sphericity was violated the Greenhouse-Geissel correction (denoted as $\varepsilon$) was applied to the degrees of freedom used to assess the observed $F$-ratio (see Table 5.4). Post hoc tests using Bonferroni correction were used to determine significant differences between times for those normally distributed continuous variables. GLM repeated measures was used to explore interactions between patients achieving SVR and non-responders and gender.

Independent sample t-tests were conducted between-groups to determine significant differences between the results of the two studies. The independent variables were inspected for multicollinearity before conducting these analyses.
Table 5.4. Mauchley’s test for sphericity and degrees of freedom corrections for PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mauchley’s W</th>
<th>Mauchley’s Test for sphericity</th>
<th>Greenhouse-Geisse correction (ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEG IFN + RBV Therapy Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Inventory (QOLI)</td>
<td>.435</td>
<td>$(x^2 (2) = 19.13, p &lt; .001)$</td>
<td>.64</td>
</tr>
<tr>
<td>Fatigue Severity Scale (FSS)</td>
<td>.395</td>
<td>$(x^2 (2) = 18.25, p &lt; .001)$</td>
<td>.53</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>.884</td>
<td>$(x^2 (2) = 2.83, p = .242)$</td>
<td>n/a</td>
</tr>
<tr>
<td>Profile of Mood States (POMS)</td>
<td>.616</td>
<td>$(x^2 (2) = 11.16, p &lt; .005)$</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Profile of Mood States: Scales</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMS-Depression/Dejection Scale</td>
<td>.455</td>
<td>$(x^2 (2) = 18.10, p &lt; .001)$</td>
<td>.65</td>
</tr>
<tr>
<td>POMS-Confusion/Bewilderment Scale</td>
<td>.792</td>
<td>$(x^2 (2) = 5.36, p = .068)$</td>
<td>n/a</td>
</tr>
<tr>
<td>POMS-Fatigue/Inertia Scale</td>
<td>.697</td>
<td>$(x^2 (2) = 8.30, p &lt; .05)$</td>
<td>.77</td>
</tr>
<tr>
<td>POMS-Tension/Anxiety Scale</td>
<td>.904</td>
<td>$(x^2 (2) = 2.32, p = .310)$</td>
<td>n/a</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>.492</td>
<td>$(x^2 (2) = 16.32, p &lt; .001)$</td>
<td>.67</td>
</tr>
<tr>
<td><strong>Hospital Anxiety &amp; Depression Scale</strong></td>
<td>.955</td>
<td>$(x^2 (2) = 1.06, p = .589)$</td>
<td>n/a</td>
</tr>
<tr>
<td>Addenbrooke's Cognitive Examination Revised</td>
<td>.994</td>
<td>$(x^2 (2) = 0.15, p = .928)$</td>
<td>n/a</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part A</td>
<td>.776</td>
<td>$(x^2 (2) = 5.85, p = .054)$</td>
<td>n/a</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part B</td>
<td>.769</td>
<td>$(x^2 (2) = 6.05, p &lt; .05)$</td>
<td>.81</td>
</tr>
<tr>
<td>Patient Satisfaction Questionnaire Short Form</td>
<td>.837</td>
<td>$(x^2 (2) = 4.09, p = .130)$</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Triple Therapy Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Inventory (QOLI)</td>
<td>.319</td>
<td>$(x^2 (2) = 29.71, p &lt; .001)$</td>
<td>.60</td>
</tr>
<tr>
<td>Fatigue Severity Scale (FSS)</td>
<td>.978</td>
<td>$(x^2 (2) = 0.55, p = .761)$</td>
<td>n/a</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>.681</td>
<td>$(x^2 (2) = 9.61, p &lt; .001)$</td>
<td>.76</td>
</tr>
<tr>
<td>Profile of Mood States (POMS)</td>
<td>.455</td>
<td>$(x^2 (2) = 10.87, p &lt; .05)$</td>
<td>.74</td>
</tr>
<tr>
<td>POMS-Depression/Dejection Scale</td>
<td>.276</td>
<td>$(x^2 (2) = 32.16, p &lt; .001)$</td>
<td>.58</td>
</tr>
<tr>
<td>POMS-Confusion/Bewilderment Scale</td>
<td>.229</td>
<td>$(x^2 (2) = 36.90, p &lt; .001)$</td>
<td>.56</td>
</tr>
<tr>
<td>POMS-Fatigue/Inertia Scale</td>
<td>.874</td>
<td>$(x^2 (2) = 3.37, p = .186)$</td>
<td>n/a</td>
</tr>
<tr>
<td>POMS-Tension/Anxiety Scale</td>
<td>.826</td>
<td>$(x^2 (2) = 4.78, p = .090)$</td>
<td>n/a</td>
</tr>
<tr>
<td>POMS-Vigour/Activity Scale</td>
<td>.464</td>
<td>$(x^2 (2) = 19.20, p &lt; .001)$</td>
<td>.65</td>
</tr>
<tr>
<td><strong>Hospital Anxiety &amp; Depression Scale</strong></td>
<td>.543</td>
<td>$(x^2 (2) = 15.28, p &lt; .001)$</td>
<td>.69</td>
</tr>
</tbody>
</table>
Table 5.4. (Cont’d) Mauchley’s test for sphericity and degrees of freedom corrections for PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mauchley’s W</th>
<th>Mauchley’s Test for sphericity</th>
<th>Greenhouse-Geiss correction ((\varepsilon))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triple therapy study (cont’d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Anxiety &amp; Depression Scale (HADS) Depression Scale(^a)</td>
<td>.765</td>
<td>((x^2(2) = 6.70, p &lt; .05))</td>
<td>.81</td>
</tr>
<tr>
<td>Hospital Anxiety &amp; Depression Scale (HADS) Anxiety Scale</td>
<td>.688</td>
<td>((x^2(2) = 9.81, p &lt; .001))</td>
<td>.76</td>
</tr>
<tr>
<td>Addenbrooke’s Cognitive Examination Revised (ACE-R)</td>
<td>.838</td>
<td>((x^2(2) = 4.43, p = .109))</td>
<td>n/a</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part A(^a)</td>
<td>.548</td>
<td>((x^2(2) = 15.05, p &lt; .05))</td>
<td>.69</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part B(^a)</td>
<td>.558</td>
<td>((x^2(2) = 14.59, p &lt; .05))</td>
<td>.69</td>
</tr>
<tr>
<td>Patient Satisfaction Questionnaire Short Form (PSQ-18)</td>
<td>.938</td>
<td>((x^2(2) = 1.61, p = .450))</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\(^a\)Mauchley’s test of sphericity violated
CHAPTER SIX:

RESULTS

This chapter will be presented in nine sections. The first section will present results on the initial exploratory data. The second section presents data at baseline on sociodemographic and clinical characteristics. The third section presents patient reported measures baseline data. The fourth section presents a comparison of patient reported measures baseline data to normative means. The fifth section will present correlations between sociodemographic and patient reported measures and between the QOL and other patient reported measures. Section six presents psychological outcomes at treatment end and three-month follow-up. Section seven discusses psychological outcomes at treatment end and three-month follow-up. Section eight discusses results of responders (SVR) and non-responders data. Finally, section nine compares psychological symptoms of SVR patients with normative population.

6.1 SECTION ONE

INITIAL EXPLORATORY DATA

Exploratory analyses were performed on the data prior to main analyses to test data entry accuracy, to identify any missing values and to test for the normality of the distribution of the variables. Data were analysed using parametric statistics which requires data to be normally distributed (Field, 2005).

6.1.1 MISSING VALUES

No missing values were observed therefore no action was required for missing values

6.1.2 OUTLIERS

Any scores falling outside of the possible range were checked for errors in data entry. Where necessary, data were re-entered to ensure correct data entry. Box plots were then examined to identify potential outliers. Influential outliers may be addressed by various
procedures which include the transformation of data, or removal of the outlier or the adjustment of the outlier so that it is one unit larger than the next largest score or one unit smaller than the next smallest score in the data set for that variable (Tabachnick & Fidell, 2005). Extreme outliers were identified in the POMS Confusion/Bewilderment subscales. These outliers were adjusted to reflect one unit larger than the next largest score or one unit smaller than the next smallest score in the data set for that variable (Tabachnick & Fidell, 2005). No other adjustments were made to the data.

6.1.3 NORMALITY OF DISTRIBUTION OF VARIABLES

Prior to analysis all data were assessed for normality and means and frequencies of demographic data were calculated. The assumption of normality was tested for all variables at all time points. The two main ways a distribution can deviate from normality are problems with skewness and kurtosis (Field, 2005). To visually obtain accurate information on the normality of distribution large samples are required, however normality of distribution can also be tested by measuring skewness and kurtosis. As a general rule, data are deemed to be normally distributed in small to moderate sized samples when values of skewness and kurtosis are within two times their standard error, or within \( \pm 1 \) of the absolute statistic (Tabachnick & Fidell, 2005). After adjusting for several extreme outliers as referenced above the skewness and kurtosis for the outcome variables were all close to the aforementioned limits. Therefore, no transformations of data were required.
6.2 SECTION TWO: 
SOCIODEMOGRAPHIC and CLINICAL STATISTICS OF PEGYLATED INTERFERON PLUS RIBAVIRIN (STUDY 1) and TRIPLE THERAPY (STUDY 2)

For the PEG IFN + RBV (Study 1), 30 patients volunteered to participate in the study all of whom met the inclusion criteria. For triple therapy (Study 2), 35 patients volunteered to participate in the study all of whom met the inclusion criteria. Prior to treatment end four (13.3%) patients withdrew from the PEG IFN + RBV (Study 1) and eight (22.9%) patients withdrew from the triple therapy (Study 2). The reasons for withdrawing from treatment were due to psychological symptoms such as depression or medical complications. One (3.3%) patient in the PEG IFN + RBV (Study 1) died after treatment end. That patient suffered from other serious illnesses which may have been the cause of death.

For the PEG IFN + RBV (Study 1), 17 (12 males, 5 females) patients achieved SVR. This represented 68% of those patients who completed treatment and 56.7% of those who started treatment. For the triple therapy (Study 2), 23 (16 males, 7 females) achieved SVR. This represented 85.2% of those patients who completed treatment and 65.7% of those who started treatment.

6.2.1. SOCIODEMOGRAPHIC AND CLINICAL STATISTICS

Baseline sociodemographic and clinical statistics for both studies are presented in Table 6.1. The baseline patient characteristics of the two therapies were closely matched. For the PEG IFN + RBV (Study 1) the mean age was 49.9 (SD = 6.89). Approximately two thirds of the participants were male (70%). The mean ages of male and female participants were 51.7 (SD = 7.47) and 46.7 (SD = 4.18) respectively. The sample was predominantly NZ European in ethnicity 26 (86.7%) with two (6.7%) Maori patients. Eighty percent of the patients were
Table 6.1. Sociodemographic and clinical statistics of PEG IFN +RBV (Study and triple therapy (2) patients.

<table>
<thead>
<tr>
<th></th>
<th>PEG IFN +RBV (Study 1) (N = 30)</th>
<th>Triple therapy (Study 2) (N = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>26(86.7%)</td>
<td>28(80.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Maori</td>
<td>2(6.7%)</td>
<td>5(14.3%)</td>
<td>p &lt;.05</td>
</tr>
<tr>
<td>Other</td>
<td>2(6.7%)</td>
<td>2(5.7%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>19(63.3%)</td>
<td>27(77.1%)</td>
<td>p &lt;.05</td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>49.9(6.89)</td>
<td>49.5(4.18)</td>
<td>ns</td>
</tr>
<tr>
<td>Male, mean (SD)</td>
<td>51.7(7.47)</td>
<td>53.3(8.42)</td>
<td>ns</td>
</tr>
<tr>
<td>Female, mean (SD)</td>
<td>46.7(4.18)</td>
<td>51.2(8.15)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Genotype:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>24(80.0%)</td>
<td>35(100.0%)</td>
<td>p &lt;.05</td>
</tr>
<tr>
<td>Type 2, 3, &amp; 6</td>
<td>6(20.0%)</td>
<td>n/a</td>
<td>p &lt;.001</td>
</tr>
<tr>
<td><strong>Marital status:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>8(26.7%)</td>
<td>10(28.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Married/Cohabitating</td>
<td>6(20.0%)</td>
<td>3(8.5%)</td>
<td>p &lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>2(6.7%)</td>
<td>4(11.4%)</td>
<td>p &lt;.05</td>
</tr>
<tr>
<td>Female</td>
<td>2(6.7%)</td>
<td>2(5.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Divorced/Separated/Widowed</td>
<td>9(30.0%)</td>
<td>8(22.8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>3(10.0%)</td>
<td>3(8.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>3(10.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary/Secondary school</td>
<td>13(43.3%)</td>
<td>13(37.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>6(20.0%)</td>
<td>4(11.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>6(20.0%)</td>
<td>9(25.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>University/ Polytechnic/Technical/Trade Certificate</td>
<td>5(16.67%)</td>
<td>4(11.4%)</td>
<td>p &lt;.05</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th></th>
<th>PEG IFN +RBV (Study 1)</th>
<th>Triple therapy (Study 2)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($N = 30$)</td>
<td>($N = 30$)</td>
<td></td>
</tr>
<tr>
<td><strong>Prescribed anti-depressants for current treatment at baseline:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male No</td>
<td>5(16.7%)</td>
<td>10(28.6%)</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Male Yes</td>
<td>14(46.7%)</td>
<td>17(48.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female No</td>
<td>3(10.0%)</td>
<td>2(5.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female Yes</td>
<td>8(26.7%)</td>
<td>6(17.1%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Methadone/marijuana use while on treatment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male No</td>
<td>16(45.7%)</td>
<td>22(62.0%)</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Male Yes</td>
<td>3(10.0%)</td>
<td>5(14.3%)</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Female No</td>
<td>9(30.0%)</td>
<td>6(17.1%)</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Female Yes</td>
<td>2(6.7%)</td>
<td>2(5.7%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>History of injecting drug use:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male No</td>
<td>4(13.3%)</td>
<td>10(28.6%)</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Male Yes</td>
<td>15(50.0%)</td>
<td>17(48.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Female No</td>
<td>10(33.4%)</td>
<td>6(17.1%)</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Female Yes</td>
<td>1(3.3%)</td>
<td>2(5.7%)</td>
<td>$p &lt; .05$</td>
</tr>
</tbody>
</table>

ns = not significant

HCV genotype 1. At the commencement of treatment 62.9% of participants were prescribed antidepressants and 25 (83.3%), comprising 15 (50.0%) males and 10 (33.3%) females reported a prior history of IV drug use, while 3 (10.0%) male and 2 (6.7%) female patients reported using methadone and/or marijuana at the commencement of treatment.

For the triple therapy study group, the mean age was 49.5 ($SD = 4.18$). Approximately eighty per cent of the patients were male (77.1%). The mean ages of male and female patients were 53.3 ($SD = 8.42$) and 51.25 ($SD = 7.30$) respectively. The sample was predominantly NZ European in ethnicity (80.0%). All patients in the triple therapy study Group were HCV genotype 1. At the commencement of treatment 65.8% of participants were prescribed antidepressants. Two thirds of participants (65.7%) reported a history of injecting drug use, while 5 (14.3%) male and 2 females (5.7%) patients reported using methadone and/or marijuana at the commencement of treatment.
6.3 SECTION THREE
PATIENT REPORTED MEASURES BASELINE DATA

6.3.1. BASELINE DATA FOR PEG IFN + RBV (STUDY 1) AND TRIPLE THERAPY (STUDY 2)

This study included the baseline data collected for the patient reported measures detailed in the Methods section. Independent samples t-tests were conducted to compare the mean scores of each of the psychological factors at baseline to determine if there were any significant differences between patients presenting for PEG IFN + RBV compared to those presenting for triple therapy. The summarised results of each reported measures baseline mean scores are set out in Table 6.2. As can be seen from Table 6.2 there were no significant differences in the mean scores of the two studies.

6.3.2. QOLI BASELINE DATA

The mean scores and standard deviations of the 16 domains of the QOLI at baseline for the PEG IFN + RBV study group and the triple therapy study group are given in Table 6.3. Independent samples t-tests were conducted to establish whether there were any differences between the two therapies for each of the domains. The definition of each QOL domain is listed in Appendix K (Quality of Life Inventory (QOLI)). The QOLI overall domain mean scores are a product of satisfaction ratings x importance ratings. A higher mean score for a domain indicates both a higher satisfaction and importance attached to the aspect of life defined by that domain by the patient. A lower mean score indicates either the aspect of life defined by domain is not important to the patient and/or the patient is not satisfied with that aspect of life.
Table 6.2 Patient reported measures baseline means (standard deviations) for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV (Study 1) Mean (SD) (N = 30)</th>
<th>Triple therapy (Study 2) Mean (SD) (N = 35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUALITY OF LIFE INVENTORY (QOLI) (Range -6 to 6)</td>
<td>1.86(0.78)</td>
<td>1.97(1.62)</td>
<td>ns</td>
</tr>
<tr>
<td>FATIGUE SEVERITY SCALE (FSS) (Range 1-7)</td>
<td>4.26(0.70)</td>
<td>5.19(1.95)</td>
<td>ns</td>
</tr>
<tr>
<td>PITTSBURGH SLEEP QUALITY INDEX (PSQI) (Range 0-21)</td>
<td>7.97(2.86)</td>
<td>7.89(3.08)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES (POMS) (Range 0-168)</td>
<td>45.90(19.76)</td>
<td>46.20(1.95)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Depression/Dejection scale</td>
<td>16.13(6.09)</td>
<td>15.65(7.11)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Confusion/Bewilderment scale</td>
<td>8.90(3.80)</td>
<td>8.89(3.23)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Anger/Hostility scale</td>
<td>8.80(5.36)</td>
<td>8.08(3.10)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Fatigue/Inertia scale</td>
<td>11.13(3.94)</td>
<td>10.89(4.58)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Tension/Anxiety scale</td>
<td>12.34(4.04)</td>
<td>12.63(4.87)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES Vigour/Activity scale</td>
<td>11.40(3.44)</td>
<td>10.82(1.64)</td>
<td>ns</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) DEPRESSION INDEX</td>
<td>5.70(2.22)</td>
<td>5.56(2.08)</td>
<td>ns</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) ANXIETY INDEX</td>
<td>6.47(2.04)</td>
<td>6.17(1.76)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns = not significant
Table 6.2 (Cont’d) Patient reported measures baseline means (standard deviations) for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV (Study 1)</th>
<th>Triple therapy (Study 2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N = 30)</td>
<td>(N = 35)</td>
<td></td>
</tr>
<tr>
<td>ADDENBROOKE’S COGNITIVE EXAMINATION REVISED (ACE-R) Range (0-100)</td>
<td>93.97(3.21)</td>
<td>93.40(4.05)</td>
<td>ns</td>
</tr>
<tr>
<td>TRAIL MAKING TEST PART A (TMT- PART A) Range (n/a)</td>
<td>34.43(9.84)</td>
<td>34.00(9.08)</td>
<td>ns</td>
</tr>
<tr>
<td>TRAIL MAKING TEST PART B (TMT- PART B) Range (n/a)</td>
<td>85.77(32.16)</td>
<td>84.14(22.72)</td>
<td>ns</td>
</tr>
<tr>
<td>PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18) Range (16-80)</td>
<td>33.87(6.91)</td>
<td>29.66(14.16)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns = not significant

For the PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI mean scores the four common domains; Relatives \( M = 2.27, M = 2.00 \), Goals \( M = 2.23, M = 2.31 \), Helping \( M = 2.17, M = 2.51 \) and Creativity \( M = 2.07, M = 2.29 \) had relatively higher mean scores than the other 12 domains. In addition, the PEG IFN + RBV (Study 1) patients reported a relatively high mean score for the domain Play \( M = 2.23 \) and triple therapy (Study 2) patients reported a relatively high score for the domain Learning \( M = 1.77 \). These scores indicate that the patients had a higher level of satisfaction and/or attached greater importance to these domains relative to the other domains (see Table 6.3 and Figure 6.1).
Table 6.3. *Comparison of means (standard deviations) PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI domains at baseline.*

<table>
<thead>
<tr>
<th>Domain</th>
<th>PEG IFN +RBV (Study 1) Mean (SD)</th>
<th>Triple therapy (Study 2) Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 30</td>
<td>N = 35</td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>1.15(1.16)</td>
<td>1.12(1.29)</td>
<td>ns</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.10(1.30)</td>
<td>1.22(1.20)</td>
<td>ns</td>
</tr>
<tr>
<td>Goals</td>
<td>2.23(0.97)</td>
<td>2.31(1.29)</td>
<td>ns</td>
</tr>
<tr>
<td>Money</td>
<td>0.93(1.91)</td>
<td>0.90(1.46)</td>
<td>ns</td>
</tr>
<tr>
<td>Work</td>
<td>1.03(1.99)</td>
<td>1.11(2.52)</td>
<td>ns</td>
</tr>
<tr>
<td>Play</td>
<td>2.23(1.63)</td>
<td>1.63(2.00)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Learning</td>
<td>1.67(0.92)</td>
<td>1.77(1.46)</td>
<td>ns</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.57(1.17)</td>
<td>1.79(1.23)</td>
<td>ns</td>
</tr>
<tr>
<td>Helping</td>
<td>1.17(1.18)</td>
<td>1.51(1.79)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Love</td>
<td>1.03(1.82)</td>
<td>1.06(2.40)</td>
<td>ns</td>
</tr>
<tr>
<td>Friends</td>
<td>1.47(2.27)</td>
<td>1.49(2.37)</td>
<td>ns</td>
</tr>
<tr>
<td>Children</td>
<td>0.73(3.26)</td>
<td>0.88(2.95)</td>
<td>ns</td>
</tr>
<tr>
<td>Relatives</td>
<td>2.27(2.11)</td>
<td>2.00(2.58)</td>
<td>ns</td>
</tr>
<tr>
<td>Home</td>
<td>1.19(2.45)</td>
<td>1.23(3.48)</td>
<td>ns</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.37(1.94)</td>
<td>1.25(2.51)</td>
<td>ns</td>
</tr>
<tr>
<td>Community</td>
<td>1.76(1.25)</td>
<td>1.54(1.01)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*ns= not significant*

Furthermore, for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) the six common domains Children (M = 0.73, M = 0.88), Money (M = 0.93, M = 0.90), Work (M = 1.03, M = 1.11), Love (M = 1.03, M = 1.06), Self-esteem (M = 1.10, M = 1.22) and Health (M = 1.15, M = 1.12) respectively, had relatively lower mean scores than the other 10 domains.
These scores indicate that the patients had a lower level of satisfaction and/or attached less importance to these domains relative to the other 10 domains (see Table 6.3 and Figure 6.1).
Table 6.4. *Comparison of means (standard deviations) PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI domain’s satisfaction ratings at baseline.*

<table>
<thead>
<tr>
<th>Domain</th>
<th>PEG IFN + RBV Mean (SD) N = 30</th>
<th>Triple therapy Mean (SD) N = 35</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>0.70(0.45)</td>
<td>0.72(0.49)</td>
<td>ns</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>0.66(0.52)</td>
<td>0.70(0.61)</td>
<td>ns</td>
</tr>
<tr>
<td>Goals</td>
<td>1.47(0.51)</td>
<td>1.60(0.77)</td>
<td>ns</td>
</tr>
<tr>
<td>Money</td>
<td>0.53(1.55)</td>
<td>0.50(1.23)</td>
<td>ns</td>
</tr>
<tr>
<td>Work</td>
<td>0.53(1.36)</td>
<td>0.62(1.43)</td>
<td>ns</td>
</tr>
<tr>
<td>Play</td>
<td>1.27(0.91)</td>
<td>1.06(1.00)</td>
<td>ns</td>
</tr>
<tr>
<td>Learning</td>
<td>1.27(0.45)</td>
<td>1.25(0.65)</td>
<td>ns</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.43(0.50)</td>
<td>1.64(0.50)</td>
<td>ns</td>
</tr>
<tr>
<td>Helping</td>
<td>1.53(0.94)</td>
<td>1.74(0.74)</td>
<td>ns</td>
</tr>
<tr>
<td>Love</td>
<td>1.37(0.93)</td>
<td>1.00(1.31)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Friends</td>
<td>1.20(1.75)</td>
<td>1.29(1.79)</td>
<td>ns</td>
</tr>
<tr>
<td>Children</td>
<td>1.01(1.94)</td>
<td>1.05(1.78)</td>
<td>ns</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.80(1.16)</td>
<td>1.98(1.60)</td>
<td>ns</td>
</tr>
<tr>
<td>Home</td>
<td>1.17(1.37)</td>
<td>1.25(1.99)</td>
<td>ns</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.00(1.20)</td>
<td>1.01(1.64)</td>
<td>ns</td>
</tr>
<tr>
<td>Community</td>
<td>1.40(0.93)</td>
<td>1.42(0.55)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns = not significant

To examine the contribution of satisfaction ratings and importance ratings to the overall QOLI mean scores (the product of Satisfaction x Importance) the correlation over the 16 items between both the satisfaction rating and the product of satisfaction and the importance rating were calculated for both PEG IFN + RBV (Study 1) and the triple therapy (Study 2). The satisfaction rating asks how satisfied a patient is with the aspects of life.
defined by the domain and importance ratings asks how important the aspects of life defined by the domain is to a patients’ happiness.

Figure 6.2. Comparison of means (standard deviations) PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI domain’s satisfaction ratings at baseline.

QOLI domain’s satisfaction ratings

The range of satisfaction ratings is -3 to +3 (-3 = very dissatisfied, -2 = somewhat dissatisfied, -1 = a little dissatisfied, +1 = a little satisfied, +2 = somewhat satisfied, +3 = very satisfied) (Frisch, 1994). Satisfaction ratings for both studies are given in Table 6.4. The correlations between the satisfaction ratings and the Importance x Satisfaction product for PEG IFN +RBV (Study 1) and triple therapy (Study 2) were 0.77 and .074 respectively. This suggests that for most patients the overall QOLI was primarily a function of satisfaction. The study found only one significant domain difference between the satisfaction ratings of the two studies. PEG IFN + RBV (Study 1) patients reported significantly more satisfaction with the domain Love than triple therapy (study 2) patients (Study 1: $M = 1.37$, $SD = 0.93$, Study 2: $M = 1.00$, $SD = 1.31$, $p < .05$).
Table 6.5. Comparison of Mean (Standard Deviation) PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI domain’s importance ratings at baseline.

<table>
<thead>
<tr>
<th>Domain</th>
<th>PEG IFN + RBV Mean (SD)</th>
<th>Triple therapy Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N = 30$</td>
<td>$N = 35$</td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>1.50(1.16)</td>
<td>1.60(1.04)</td>
<td>ns</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.53(1.30)</td>
<td>1.63(1.13)</td>
<td>ns</td>
</tr>
<tr>
<td>Goals</td>
<td>1.57(0.97)</td>
<td>1.57(0.89)</td>
<td>ns</td>
</tr>
<tr>
<td>Money</td>
<td>0.50(1.91)</td>
<td>0.53(1.56)</td>
<td>ns</td>
</tr>
<tr>
<td>Work</td>
<td>0.76(1.99)</td>
<td>0.80(1.69)</td>
<td>ns</td>
</tr>
<tr>
<td>Play</td>
<td>1.25(1.63)</td>
<td>1.66(1.53)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Learning</td>
<td>1.40(0.92)</td>
<td>1.26(0.93)</td>
<td>ns</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.13(1.17)</td>
<td>1.23(1.28)</td>
<td>ns</td>
</tr>
<tr>
<td>Helping</td>
<td>1.00(1.18)</td>
<td>0.95(1.10)</td>
<td>ns</td>
</tr>
<tr>
<td>Love</td>
<td>0.83(1.82)</td>
<td>0.94(1.71)</td>
<td>ns</td>
</tr>
<tr>
<td>Friends</td>
<td>1.67(1.27)</td>
<td>1.69(1.56)</td>
<td>ns</td>
</tr>
<tr>
<td>Children</td>
<td>0.55(1.26)</td>
<td>0.54(1.21)</td>
<td>ns</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.50(1.11)</td>
<td>1.40(1.16)</td>
<td>ns</td>
</tr>
<tr>
<td>Home</td>
<td>1.12(1.45)</td>
<td>1.10(1.26)</td>
<td>ns</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.05(1.94)</td>
<td>1.00(1.79)</td>
<td>ns</td>
</tr>
<tr>
<td>Community</td>
<td>1.04(1.25)</td>
<td>1.05(0.68)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns = not significant

Mean satisfaction ratings for each domain in the QOLI for both therapies at baseline were examined and found that respectively for PEG IFN + RBV (Study 1) and triple therapy, Relatives ($M = 1.80, M = 1.98$), Helping ($M = 1.53, M = 1.74$), Goals ($M = 1.47, M = 1.60$) and Creativity ($M = 1.43, M = 1.64$) had relatively higher satisfaction ratings than the 12 other domains, and the domains Money ($M = 0.53, M = 0.50$), Work ($M = 0.53, M = 0.62$),
Self-esteem ($M = 0.66, M = 0.70$) and Health ($M = 0.70, M = 0.72$) had relatively lower satisfaction ratings than the other 12 domains.

**QOLI domain’s importance ratings**

The range for mean importance ratings is 0 to 2 (0 = not important at all, 1 = important, 2 = extremely important (Frisch, 1994)). The baseline correlation for PEG IFN + RBV (Study 1) and triple therapy (Study 2) and the Importance x Satisfaction product was 0.27 and 0.20 respectively. The domain Play was reported as significantly more important to triple therapy (Study 2) patients than for PEG IFN + RBV (Study 1) patients (Study 2: $M = 1.66, SD = 1.53$, Study 1: $M = 1.25, SD = 1.63$, $p < .05$). There were no other significant differences between the two study’s baseline means for importance ratings (see Table 6.5 and Figure 6.3).

**Figure 6.3.** Comparison of Mean (Standard Deviation) PEG IFN + RBV (Study 1) and triple therapy (Study 2) QOLI domain’s importance ratings at baseline.

Mean importance ratings for each domain in the QOLI for both therapies at baseline were examined. It was found that respectively for PEG IFN + RBV (Study 1) and triple
therapy (Study 2), Friends (M = 1.67, M = 1.69), Goals (M = 1.57, M = 1.57), Self-esteem (M = 1.53, M = 1.63), Health (M = 1.50, M = 1.60), and Relatives (M = 1.50, M = 1.40) had relatively higher importance ratings than the 11 other domains, and the domains Money (M = 0.50, M = 0.53), Children (M = 0.55, M = 0.54), Work (M = 0.75, M = 0.80) and Love (M = 0.83, M = 0.94) had relatively lower importance ratings than the 12 other domains.

The domains with the relatively higher importance ratings were examined to find whether those domains were also domains with relatively lower satisfaction ratings (see Tables 6.6 and 6.7). It was found that respectively for PEG IFN + RBV (Study 1) and triple therapy (Study 2) the domains Health (importance ratings M = 1.50, M = 1.60; satisfaction ratings M = 0.70, M = 0.72) and Self-esteem (importance ratings M = 1.53, M = 1.63; satisfaction ratings M = 0.66, M = 0.70) had relatively high importance ratings but relatively low satisfaction ratings. For both studies the importance ratings for the Health and Self-esteem domains were between “important” to “very important”, but the satisfaction ratings for the 2 domains were between “no satisfaction” and “a little satisfaction”. Ten domains (Friends, Goals, Relatives, Home, Neighbourhood, Learning, Play, Helping, Community and Creativity) indicated importance ratings between “important” and “extremely important” with satisfaction ratings between “a little satisfied” to “somewhat satisfied”. For both studies the importance rating for four domains (money, children, work, home) were between the importance ratings “not at all important” and “important”.

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6.4 SECTION FOUR

COMPARISON OF PATIENT REPORTED MEASURES
BASELINE DATA TO NORMATIVE MEANS

The baseline data for each of these measures was analysed separately and compared to normative means for each measure used in the study. Means used in section 6.4 are unadjusted means.

Hypothesis 1.

The psychological symptoms reported by patients presenting for PEG IFN + RBV therapy and triple therapy will be poorer than other norm referenced clinical populations of the standardized measures of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, and cognitive function.

6.4.1 QUALITY OF LIFE (QOL)

The overall mean QOLI score reported by the patients in the PEG IFN + RBV (Study 1) and the triple therapy (Study 2) were 1.86 ($SD = 0.78$) and 1.97 ($SD = 1.62$) respectively. The possible range of scores for the QOLI is -6 to 6, with a higher mean score indicating a person is reporting a better QOL. QOLI scores of between 2 and 3.75 represent typical scores for adults. Scores outside of this range may be viewed as significantly above or below average (Frisch et al., 1992). The mean scores of 1.86 and 1.97 reported for the PEG IFN + RBV (Study 1) and the triple therapy (Study 2) respectively are below the range representing typical scores for adults.
6.4.2 FATIGUE AND SLEEP DISORDERS

The mean score for the FSS measure of fatigue for healthy adults is 2.30. A higher score on the FSS measure represents a higher level of fatigue. The FSS mean score reported by patients in PEG IFN + RBV (Study 1) and triple therapy (Study 2) at baseline were 4.26 (SD = 0.70) and 5.19 (SD = 1.95) respectively. The difference in FSS mean scores between the two studies was not significant. These mean scores compare to a mean score of 2.30 (SD = 0.70) for healthy adults (Grace, Mendelsohn, & Friedman, 2007), 4.50 for respondents with depression alone (without fatigue associated conditions), and 6.50 for persons with fatigue related to illnesses such as multiple sclerosis (MS), systemic lupus erythematosus (SLE) and chronic fatigue immune dysfunction syndrome (CFIDS) (Krupp et al., 1989) (see Figure 6.4). A mean score of 4.34 (SD = 1.64) has been reported for patients with sleep-wake disorders (Valko et al., 2008) It has been suggested that a mean score of ≥ 4 be interpreted as an indication of fatigue (Valko et al., 2008).

A 2001 study reported the optimal FSS cut off for clinically significant fatigue was a mean score of 5.4 (Ferentinos, Kontaxakis, Havaki-Kontaxaki, Dikeos, & Lykouras, 2011) (see Figure 6.4). At baseline 12 (40.0%) patients in the PEG IFN + RBV (Study 1) and 24 (68.6%) in the triple therapy (Study 2) reported mean scores higher than 4.50 (the normative mean cut-off score for depression alone). A further five patients (16.7%) and 2 (5.7%) for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) respectively neared the mean score of 4.50. Of the 12 patients in the PEG IFN + RBV (Study 1) scoring above a mean of 4.50, seven patients (representing 23.3% of the 35 baseline patients) reported a mean score above 6.50. Of the 24 patients in the triple therapy (Study 2) scoring above 4.50, and 12 patients (34.3% of the 35 baseline patients) scored more than a 6.6 mean score.

The POMS Fatigue/Inertia scale was also used to measure fatigue. It was found that PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients reported mean scores of
11.13 (SD = 3.94) and 10.89 (SD = 4.58) respectively in comparison to normative means of 7.30 (SD = 5.70) for normative adult population (Nyenhuis, Yamamoto, Luchetta, Terrien, & Parmentier, 1999) and 11.0 for patients suffering from pain.

The mean baseline scores reported by patients in the PEG IFN + RBV (Study 1) and the triple therapy (Study 2) for the PSQI sleep measure were 7.97 (SD = 2.86) and 7.89 (SD = 3.08) respectively. The difference in mean scores between each study group was not significant for both unadjusted and mean scores. A PSQI mean score for normal sleep is 2.67 (SD =1.70) (Buysse et al., 1989), with higher scores indicating potential sleep disorders. At baseline all the patients in PEG IFN + RBV (Study 1) and 33 (94.3%) of the triple therapy (Study 2) reported PSQI mean scores which exceeded a 2.67 score. Figure 6.5 presents an

Figure 6.4. Comparison of the PEG IFN + RBV (Study 1) and triple therapy (Study 2) FSS baseline means to FSS normative means for healthy adults, sleep-wake disorders, clinically significant fatigue and fatigue related illnesses.
overview of relevant normative PSQI cut off mean scores compared to the two study’s PSQI mean scores. This highlights that for both PEG IFN + RBV (Study 1) and triple therapy (Study 2) the mean scores were above that of disorders of excessive daytime somnolence. Furthermore, at baseline for the PEG IFN + RBV (Study 1) and the triple therapy (Study 2), five (16.7%) and 4(11.4%) respectively scored above the 12.50 cut-off for primary insomnia, 6 (20.0%) and 4 (11.4%) respectively scored higher than the 11.09 cut-off for major depression, 7(23.3%) and 12 (34.5%) respectively scored above the 10.38 cut-off for disorders of initiating and maintaining sleep and 17 (56.6%) and 21 (60.0%) respectively scored above the 6.53 cut-off for disorders of excessive daytime somnolence.

Figure 6.5. Comparison of PSQI means for PEG IFN + RBV (Study 1) and triple therapy (Study 2) to PSQI means for normal sleep, disorders of excessive daytime somnolence, major depression, and primary insomnia.
The PSQI mean scores for the Heeren and colleagues (2014) study were 13 (range 8.25-16) for HCV-infected patients pre-treatment and 5 (range 3-7) for healthy controls. The PSQI mean score in the Yoh and colleagues (2016) study of CHC patients prior to PEG IFN + RBV + SMV triple therapy was 3.5 (range 1 to 15).

6.4.3 MOOD DISTURBANCE

Total Mood Disturbance (TMD) is calculated as the sum of the scales DD+AH+CB++FI+TA less the VA scale). The baseline POMS Total Mood Disturbance (TMD) mean scores reported by the PEG IFN + RBV (Study 1) and triple therapy (Study 2) were 45.90 (SD =19.76) and 46.20 (SD = 21.79) respectively. This result compares to a TMD normative mean of 12.70 (SD = 29.60) for the adult population.

A comparison of the separate POMS baseline scale mean scores for both the PEG IFN + RBV (Study 1), triple therapy (Study 2), normative adult population (Nyenhuis et al., 1999), and geriatric patients suffering from chronic pain reported in the Gibson (1997) study is set out in Figure 6.6. A higher POMS scale mean score indicates a higher level of impairment except for the Vigour/Activity scale mean score in which the inverse applies.

Overall the mean scores reported for both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) indicates greater impairment in all of the scale’s mean scores compared to the scales’ mean scores for normative adult population. When compared to the scale’s mean scores for pain patients, the PEG IFN + RBV (Study 1) shows a higher mean score for the Depression /Dejection, Anger/ Hostility, and Confusion/Bewilderment scales. Scores on the Fatigue/ Inertia scale were similar to pain patients, but were lower on the Tension/Anxiety scale. Lower mean scores were reported on the Vigour/Activity scale.

Furthermore, when compared to the mean scores for pain patients, the triple therapy study group shows a higher mean score on the Depression/Dejection and Confusion/ Bewilderment scales. Scores on the Anger/Hostility and Fatigue/ Inertia scales were similar.
to pain patients, but were lower on the Tension/Anxiety scale. Lower mean scores were reported on the Vigour/Activity scale by patients in triple therapy (Study 2).

![Comparison of POMS scale means to POMS scale's means in normative adult population (Nyenhuis et al., 1999), and geriatric patients suffering from chronic pain (Gibson, 1997).](image)

**Figure 6.6.** Comparison of PEG IFN + RBV (Study 1) and triple therapy (Study 2) baseline POMS scale’ means to POMS scale’s means in normative adult population (Nyenhuis et al., 1999), and geriatric patients suffering from chronic pain (Gibson, 1997).

### DEPRESSION AND ANXIETY

The HADS Depression scale mean score reported at baseline were 5.70 ($SD = 2.22$) and 5.26 ($SD = 2.08$) for PEG IFN + RBV (Study 1) and the triple therapy (Study 2) respectively. Scores between 0 and 7 are treated as normal while scores between 8 and 10 are an indication of possible clinical depression (Zigmond & Snaith, 1983). At baseline 5(16.7%)
and 5(14.2%) of PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients, respectively scored between 8 and 10, meeting the criteria for current major depressive disorder and a further 11(36.7%) and 11(31.4%) respectively neared the cut off score of 8. Higher scores in the HADS depression scale represent higher levels of depression.

Furthermore, depression was measured by the POMS Depression/Dejection scale. It was found the PEG IFN + RBV (Study 1) and triple therapy (Study 2) reported mean scores of 16.13 ($SD = 6.09$) and 15.65 ($SD = 7.11$) respectively in comparison to normative means of 7.10 ($SD = 8.40$) for normative adult population and 15.00 ($SD = 8.25$) for patients suffering from pain (see Figure 6.6).

The HADS Anxiety scale mean score at baseline was 6.47 ($SD = 2.04$) and 6.17 ($SD = 1.76$) respectively for the PEG IFN + RBV (Study 1) and the triple therapy (Study 2). Similar to the Depression Scale mean scores between 0 and 7 are treated as normal while mean scores between 8 and 10 are an indication of possible clinical anxiety (Zigmond & Snaith, 1983). At baseline 4(13.4%) and 13(37.1%) respectively of PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients scored between 8 and 10 and a further 10(33.4%) and 6(17.1%) respectively neared the cut off score of 8. Higher scores in the HADS anxiety scale represent higher levels of anxiety.

Furthermore, anxiety was measured by the POMS Tension/Anxiety scale. It was found the PEG IFN + RBV (Study 1) and triple therapy (Study 2) reported mean scores of 12.34 ($SD = 4.04$) and 12.63 ($SD = 4.87$) respectively in comparison to normative means of 7.00 ($SD = 5.50$) for normative adult population and 14.0 for patients suffering from pain (see Figure 6.6).

6.4.5 COGNITIVE FUNCTIONING

Patient’s cognitive functioning was measured using the ACE-R and the TMT Parts A and B. The ACE-R overall mean scores reported at baseline for the PEG IFN + RBV therapy
(Study 1) and the triple therapy (Study 2) were 93.97 (SD = 3.21) and 91.37 (SD = 4.05) respectively compared to a normative mean score of 96.0 (SD = 2.70). Higher ACE-R scores represent better cognitive function. The ACE-R comprises 5 factors: Attention /Orientation, Memory, Verbal fluency, Language, and Visuospatial. The baseline scores of these factors and normative scores are set out in Table 6.8.

For both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) there was an overall significance ($p < .05$) impairment to normative mean scores as measured by the ACE-R. Furthermore, the factors Memory and Verbal Fluency showed significant ($p < .05$) impairment for both groups when compared to the normative mean scores for those two factors. For both PEG IFN + RBV (Study 1) and triple therapy (Study 2) the other three factors comprising the ACE-R showed no significant difference to normative mean scores (see Table 6.6).

The main contributor to a lower memory factor score at baseline, for both studies was in the second recall question of the memory factor of the questionnaire. All patients answered all of the first memory recall, anterograde memory and retrograde memory questions correctly but had difficulty recalling at the end of the questionnaire the name and address which had been repeated at the beginning of the questionnaire. The other factor of the questionnaire that patients in both studies scored lower than the normative score was verbal fluency. Patients were asked to list as many words starting with the letter P within a minute. They were also asked to list separately, within a minute, as many animals as they could. This factor had a possible score of 14, but 7 (23.3%) patients and 10 (28.6%) patients in PEG IFN + RBV (Study 1) and triple therapy (Study 2) respectively scored less than 10 from the possible 14. Other than these two factors of the ACE-R baseline patients mean scores for both studies were similar to the normative mean ACE-R scores.
Mean baseline scores for the TMT Part A and TMT Part B were 34.43 seconds ($SD = 9.84$) and 85.77 seconds ($SD = 32.16$) respectively for the PEG IFN + RBV (Study 1) and 34.00 seconds ($SD = 9.08$) and 84.14 seconds ($SD = 22.72$) respectively for the triple therapy (Study 2). Both PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients took significantly ($p < .05$) longer to complete the TMT Part A than the normative average scores of 29 seconds and significantly ($p < .05$) longer that the normative 75 seconds to complete the TMT Part B. However, both study group’s mean baseline scores were significantly ($p < .05$) less than scores determined as being “deficient” (> 78 seconds and >273 seconds respectively) and “Rule of Thumb” scores (> 90 seconds and > 3 minutes) respectively.

Table 6.6. **ACE-R baseline mean ($SD$) and normative mean ($SD$) for PEG IFN + RBV (Study 1) and triple therapy (Study 2).**

<table>
<thead>
<tr>
<th>Factor</th>
<th>PEG IFN + RBV (Study 1)</th>
<th>Triple Therapy (Study 2)</th>
<th>Normative mean</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Mean (Standard deviation)</td>
<td>Mean (Standard deviation) (Standard deviation)</td>
<td></td>
</tr>
<tr>
<td>N = 30</td>
<td>N = 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/Orientation</td>
<td>17.93 (0.36)</td>
<td>17.90 (0.40)</td>
<td>17.60 (0.60)</td>
</tr>
<tr>
<td>Memory</td>
<td>23.03 (1.45)*</td>
<td>23.10 (1.25)*</td>
<td>24.60 (1.20)</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>11.83 (2.65)*</td>
<td>11.50 (2.10)*</td>
<td>12.60 (1.10)</td>
</tr>
<tr>
<td>Language</td>
<td>25.93 (0.25)</td>
<td>25.80 (0.42)</td>
<td>25.30 (0.90)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>15.23 (0.62)</td>
<td>15.20 (0.65)</td>
<td>15.50 (0.70)</td>
</tr>
<tr>
<td>Total ACE-R</td>
<td>93.97 (3.21)*</td>
<td>93.40 (4.05)*</td>
<td>96.00 (2.70)</td>
</tr>
</tbody>
</table>

*Significant difference ($p < .05$) to normative mean

6.4.6 **PATIENT SATISFACTION**

Patient satisfaction reported by patients at baseline were 33.87 ($SD = 6.91$) and 29.66 ($SD = 14.16$) for the PEG IFN +RBV (Study 1) and the triple therapy (Study 2) respectively. The range of possible scores for the PSQ-18 excluding the two financial aspect questions in this study was 16 to 80 with a higher score indicating more dissatisfaction with medical treatment. The normal mean score for the PSQ-18 for the same questions used in this study
was 50.20 (SD = 11.67), indicating the patients for both studies were more satisfied with their medical treatment than would be expected in a normative population presenting for a medical treatment.

6.5 SECTION FIVE
CORRELATIONS

6.5.1 CORRELATION BETWEEN PSYCHOLOGICAL SYMPTOMS AND SOCIO–DEMOGRAPHICS AT BASELINE FOR PEG IFN + RBV THERAPY (STUDY 1) AND TRIPLE THERAPY (STUDY 2)

Hypothesis 2:

There will be no association between socio-demographic factors at baseline and the severity of symptoms reported by patients presenting for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

For the combined PEG IFN + RBV (Study 1) and triple therapy (Study 2) Pearson’s correlations coefficients were computed to investigate the relationships at baseline between patient’s socio-demographic factors and the psychological symptoms: QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, and cognitive function (see Table 6.7). The socio-demographic factors used in Pearson’s correlation were: age, marital status, educational level, prescribed antidepressants for treatment, current use of marijuana or methadone or other non-prescription drugs and a history of injecting drug use. Since a significant majority of patients were of European Caucasian ethnicity and HCV genotype 1, the factors of ethnicity and genotype were not entered into the correlation model.

As expected, there was no association between the socio-demographic factors of patients presenting for PEG IFN + RBV (Study 1) and triple therapy (Study 2) and the psychological symptoms: QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function, and patient satisfaction.
Table 6.7. Correlations at baseline between psychological symptoms of PEG IFN + RBV (Study 1) and triple therapy (Study 2) and socio-demographics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Gender</th>
<th>Age</th>
<th>Marital status</th>
<th>Education level</th>
<th>Anti-depressants at baseline</th>
<th>Marijuana use baseline</th>
<th>Injecting drug use history</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
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<td>.00</td>
<td>.12</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
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<td>.25</td>
<td>.01</td>
<td>.06</td>
<td>.10</td>
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<td>.00</td>
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<td>.05</td>
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<td>.12</td>
<td>.05</td>
</tr>
<tr>
<td>POMS-TMD</td>
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<td>.07</td>
<td>.08</td>
<td>.01</td>
<td>.07</td>
<td>.12</td>
<td>.05</td>
</tr>
<tr>
<td>POMS (D/D scale)</td>
<td>.18</td>
<td>.15</td>
<td>.11</td>
<td>.04</td>
<td>.11</td>
<td>.08</td>
<td>.15</td>
</tr>
<tr>
<td>POMS (C/B scale)</td>
<td>.12</td>
<td>.14</td>
<td>.07</td>
<td>.05</td>
<td>.12</td>
<td>.07</td>
<td>.07</td>
</tr>
<tr>
<td>POMS (A/H scale)</td>
<td>.13</td>
<td>.07</td>
<td>.04</td>
<td>.01</td>
<td>.12</td>
<td>.06</td>
<td>.09</td>
</tr>
<tr>
<td>POMS (F/H scale)</td>
<td>.19</td>
<td>.11</td>
<td>.01</td>
<td>.03</td>
<td>.10</td>
<td>.07</td>
<td>.00</td>
</tr>
<tr>
<td>POMS (G/A scale)</td>
<td>.17</td>
<td>.12</td>
<td>.04</td>
<td>.02</td>
<td>.10</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>POMS (V/A scale)</td>
<td>.15</td>
<td>.01</td>
<td>.02</td>
<td>.03</td>
<td>.05</td>
<td>.11</td>
<td>.05</td>
</tr>
<tr>
<td>HADS (Depression scale)</td>
<td>.19</td>
<td>.14</td>
<td>.10</td>
<td>.01</td>
<td>.11</td>
<td>.09</td>
<td>.05</td>
</tr>
<tr>
<td>HADS (Anxiety scale)</td>
<td>.17</td>
<td>.08</td>
<td>.05</td>
<td>.02</td>
<td>.10</td>
<td>.07</td>
<td>.11</td>
</tr>
<tr>
<td>ACE-R</td>
<td>.21</td>
<td>.10</td>
<td>.05</td>
<td>.15</td>
<td>.08</td>
<td>.11</td>
<td>.05</td>
</tr>
<tr>
<td>TMT (Part A)</td>
<td>.01</td>
<td>.02</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>TMT (Part B)</td>
<td>.15</td>
<td>.10</td>
<td>.02</td>
<td>.11</td>
<td>.11</td>
<td>.09</td>
<td>.07</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>.02</td>
<td>.03</td>
<td>.02</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.03</td>
</tr>
</tbody>
</table>
Table 6.8. *Correlation matrix: QOL and psychological symptoms at baseline for PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2).*

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV therapy (Study 1) QOLI (N = 30)</th>
<th>Triple therapy (Study 2) QOLI (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue Severity Scale (FSS)</td>
<td>-.60**</td>
<td>-.65**</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>-.49**</td>
<td>-.48**</td>
</tr>
<tr>
<td>Profile of Mood States (POMS) TMD</td>
<td>-.51**</td>
<td>-.45**</td>
</tr>
<tr>
<td>Profile of Mood States: Scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMS-Depression/Dejection Scale</td>
<td>-.74**</td>
<td>-.70**</td>
</tr>
<tr>
<td>POMS-Anger/Hostility Scale</td>
<td>-.41*</td>
<td>-.40*</td>
</tr>
<tr>
<td>POMS-Confusion/Bewilderment Scale</td>
<td>-.52**</td>
<td>-.50**</td>
</tr>
<tr>
<td>POMS-Fatigue/Inertia Scale</td>
<td>-.52**</td>
<td>-.51**</td>
</tr>
<tr>
<td>POMS-Tension/Anxiety Scale</td>
<td>-.66**</td>
<td>-.66**</td>
</tr>
<tr>
<td>POMS-Vigour/Activity Scale</td>
<td>.24</td>
<td>.20</td>
</tr>
<tr>
<td>Hospital Anxiety &amp; Depression Scale (HADS) Depression Scale</td>
<td>-.61**</td>
<td>-.55**</td>
</tr>
<tr>
<td>Hospital Anxiety &amp; Depression Scale (HADS) Anxiety Scale</td>
<td>-.64*</td>
<td>-.60**</td>
</tr>
<tr>
<td>Addenbrooke's Cognitive Examination Revised (ACE-R)</td>
<td>.43**</td>
<td>.43**</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part A</td>
<td>-.03.</td>
<td>-.05</td>
</tr>
<tr>
<td>Trail Making Test (TMT)-Part B</td>
<td>-.40*</td>
<td>-.41*</td>
</tr>
<tr>
<td>Patient Satisfaction Questionnaire Short Form (PSQ-18)</td>
<td>.09</td>
<td>-.11</td>
</tr>
</tbody>
</table>

* *p < .05, ** *p < .001
6.5.2 CORRELATION BETWEEN QOL AND OTHER PSYCHOLOGICAL SYMPTOMS AT BASELINE FOR PEG IFN + RBV (STUDY 1) AND TRIPLE THERAPY (STUDY 2).

Hypothesis 3:

There will a significant correlation between QOL, as a measure of satisfaction, and psychological symptoms including fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function, and patient satisfaction at baseline for patients presenting for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

Pearson’s correlations coefficients were computed to investigate the relationships between: QOL and fatigue, sleep disorders, mood state disturbances, depression, and anxiety at baseline for PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients. The results of these analyses are presented in Table 6.8. There was a significant negative relationship between QOL and fatigue, sleep, POMS (Total mood disturbance (TMD), POMS Depression/Dejection scale, POMS Confusion/Bewilderment scale, POMS Tension/Anxiety scale) and depression and anxiety ($p < .001$). There was also a significant relationship between QOL and cognitive function as measured by ACE-R ($p < .001$) and TMT Part B ($p < .05$). Furthermore, the negative relationship between QOL and the POMS Anger/Hostility scale neared significance ($r = -.36, p = .06$). There was no relationship between QOL and the POMS Vigour/Activity scale, nor the TMT Part A, nor patient satisfaction.

The negative correlation between QOL and the psychological symptoms referred to above indicates that when patients reported a decrease in QOL there was an increase in psychological symptoms. Furthermore, the relationship between QOL and cognitive skills indicates that with a decrease in QOL there is a decrease in cognitive skills as measured by ACE-R and TMT Part B. There was no relationship between QOL and the TMT A which requires less cognitive skills that the TMT Part B. This result indicates that changes in QOL are significantly related to cognitive functions requiring a higher level of cognitive skills. The more simpler cognitive skills as tested by the TMT Part A are not related to changes in QOL.
The correlation analysis for triple therapy (Study 2) showed similar relationships as for the PEG IFN + RBV (Study 1). The original hypothesis in relation to this section stated that there would be a significant correlation between the QOL and psychological symptoms, including fatigue, sleep disorders, mood state disturbances, depression, anxiety and cognitive function and patient satisfaction for both the PEG IFN + RBV (Study 1) and triple therapy (Study 2). Taken together the results support the hypothesis except for patient satisfaction.

Table 6.10: Correlation matrix: QOL and psychological symptoms at baseline for PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2).

The correlations reported between QOL and psychological symptoms at baseline were also similar to the correlations between QOL and psychological symptoms at treatment end and a three-months follow-up for both studies.

Furthermore, for both studies at baseline, treatment end and at three-month follow-up, there was a significant relationship between fatigue, sleep, POMS (TMD, all of the POMS scales except the Vigour/Activity scale), depression and anxiety. Also, for both studies and for the three time periods cognitive function as measured by ACE -R was significantly or neared significance, negatively related to fatigue, sleep, all of the POMS scales, depression, and anxiety. For both studies the TMT Part A was not related with any psychological symptoms for any time points. For the PEG IFN + RBV (Study 1) and triple therapy (Study 2) the TMT Part B was significantly negatively related to Sleep, POMS (Anger/Hostility, Confusion/ Bewilderment, and Tension/Anxiety scales) and anxiety for all time points. This result again highlights that patients have more difficulty with cognitive functions requiring a higher level of skill and concentration. Finally, patient satisfaction was not related to any psychological symptoms, at any timepoint for either study.
6.6 SECTION SIX

PSYCHOLOGICAL OUTCOMES AT TREATMENT END AND THREE-MONTH FOLLOW-UP

The change in psychological symptoms at end of treatment and at 3-month follow-up after treatment for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) were analysed using GLM within group repeated measures and are presented under each of the relevant psychological symptoms. Mauchly’s test and the violation of assumption of sphericity, and where assumptions have been violated, the degrees of freedom corrections, for each of the measures for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) are set out in Table 5.5 (see Chapter 5, Section 5.6, Data Analysis). The means presented in this section are adjusted means.

Hypothesis 4:

*Patients being treated with PEG IFN + RBV (Study 1) and triple therapy (Study 2) will report significantly more impairment of psychological symptoms at treatment end compared to pre-treatment (baseline), but will report a return to pre-treatment (baseline) levels of psychological symptoms at 3-month follow-up to treatment end.*

The mean scores and standard deviations of the PEG IFN + RBV (Study 1) and the triple therapy (Study 2) are set out in Tables 6.11 and 6.13 respectively. The mean differences in baseline, treatment end and 3-month follow-up are set out in Table 6.10 and 6.12 respectively. Mauchly’s test and the violation of assumption of sphericity, (and where assumptions have been violated, the degrees of freedom corrections) for each of the measures for both the PEG IFN + RBV (Study 1) and are set out in Table 5.5 (see Chapter 5, Section 5.6, Data Analysis). The means presented in this section are adjusted means.
For the PEG IFN + RBV (Study 1) thirty patients completed the questionnaire at baseline. Four patients withdrew from treatment before scheduled treatment end date, and one patient died after completing the questionnaire at treatment end, but before the three-month follow-up. Overall there was a significant increase in the impairment of all psychological symptoms at treatment end compared to baseline except for the psychological symptoms measured by POMS Confusion/ Bewilderment scale, the Trail Making Tests Part A and Part B and the Patient Satisfaction Questionnaire (see Table 6.10). At three-month follow-up to treatment end there was a significant improvement of psychological symptoms compared to treatment end for all psychological symptoms measured except for TMT Part A and patient satisfaction. Furthermore QOL, the Vigour/Activity POMS scale and the Trail Making Test Part B. For all other psychological symptoms measured (see Table 6.10). Furthermore, there was a significant impairment of psychological symptoms at three-month follow-up to treatment end compared to baseline for: QOL, fatigue, sleep, vigour/activity and both the TMT Part A and Part B. However, there was a significant improvement of psychological symptoms at three-month follow-up compared to baseline for the two POMS scales Anger/Hostility and Tension/Anxiety.
Table 6.9 *Patient reported measures adjusted means (standard deviations) for the PEG IFN + RBV (Study 1) at baseline, treatment end and 3-month follow-up*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (SD) N=30</th>
<th>Treatment end Mean (SD) N=26</th>
<th>3-month follow-up Mean (SD) N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUALITY OF LIFE INVENTORY (QOLI) (Range -6 to 6)</td>
<td>1.96(0.72)</td>
<td>1.03(0.44)</td>
<td>1.85(0.67)</td>
</tr>
<tr>
<td>FATIGUE SEVERITY SCALE (FSS) (Range 1-7)</td>
<td>4.32(1.82)</td>
<td>5.25(1.29)</td>
<td>5.25(1.28)</td>
</tr>
<tr>
<td>PITTSBURGH SLEEP QUALITY INDEX (PSQI) (Range 0-21)</td>
<td>7.76(2.88)</td>
<td>10.82(3.02)</td>
<td>8.32(2.14)</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES (POMS) (Range 0-168)</td>
<td>44.12(20.35)</td>
<td>58.76(14.35)</td>
<td>15.33(3.79)</td>
</tr>
<tr>
<td>Depression/Dejection scale</td>
<td>15.88(6.11)</td>
<td>19.00(8.50)</td>
<td>7.68(0.49)</td>
</tr>
<tr>
<td>Anger/Hostility scale</td>
<td>8.32(5.36)</td>
<td>10.57(2.67)</td>
<td>7.68(0.49)</td>
</tr>
<tr>
<td>Confusion/Bewilderment scale</td>
<td>8.56(3.95)</td>
<td>9.70(2.48)</td>
<td>9.52(2.98)</td>
</tr>
<tr>
<td>Fatigue/Inertia scale</td>
<td>10.52(4.12)</td>
<td>12.95(2.35)</td>
<td>12.01(2.93)</td>
</tr>
<tr>
<td>Tension/Anxiety scale</td>
<td>12.22(4.09)</td>
<td>14.02(2.48)</td>
<td>11.49(3.63)</td>
</tr>
<tr>
<td>Vigour/Activity scale</td>
<td>11.64(3.68)</td>
<td>8.12(1.67)</td>
<td>9.99(2.36)</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) DEPRESSION INDEX Range (0-21)</td>
<td>5.56(2.31)</td>
<td>7.28(1.77)</td>
<td>5.40(1.35)</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) ANXIETY INDEX Range (0-21)</td>
<td>6.36(2.06)</td>
<td>8.16(1.76)</td>
<td>6.40(2.02)</td>
</tr>
</tbody>
</table>
Table 6.9 (Cont’d). *Patient reported measures adjusted means (standard deviations) for the PEG IFN + RBV (Study 1) at baseline, treatment end and 3-month follow-up*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Treatment end</th>
<th>3-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) N =30</td>
<td>Mean (SD) N =26</td>
<td>Mean (SD) N =25</td>
</tr>
<tr>
<td>ADDENBROOKE’S COGNITIVE EXAMINATION REVISED (ACE-R)</td>
<td>93.92(3.49)</td>
<td>92.44(3.36)</td>
<td>94.36(2.58)</td>
</tr>
<tr>
<td>(Range (0-100))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAIL MAKING TEST PART A (TMT- PART A) (Range (n/a))</td>
<td>34.76(10.65)</td>
<td>34.76(11.06)</td>
<td>33.20(9.55)</td>
</tr>
<tr>
<td>PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18) (Range (16.-80))</td>
<td>32.88(6.48)</td>
<td>33.28(8.07)</td>
<td>35.44(6.92)</td>
</tr>
</tbody>
</table>

For triple therapy (Study 2) thirty-five patients completed the questionnaire at baseline. Eight patients withdrew from treatment before scheduled treatment end date.

Overall there was a significant increase in the impairment of all psychological symptoms at treatment end compared to baseline except for Patient Satisfaction and the TMT Part A (see Table 6.12). At three-month follow-up to treatment end there was a significant improvement in the psychological symptoms compared to treatment end for all psychological symptoms measured except for the POMS Confusion/Bewilderment scale, the HADS depression scale, the TMT Part A and patient satisfaction (see Table 6.12).

Furthermore, there was a significant impairment of psychological symptoms at three-month follow-up compared to baseline for: QOL, fatigue and sleep. However, there was a significant improvement of psychological symptoms at three-month follow-up compared to baseline for the three POMS scales Anger/Hostility, Tension/Anxiety, and Vigour/Activity (see Table 6.12).
Table 6.10: Mean differences in baseline, treatment end and 3-month follow-up (adjusted means) for PEG IFN + RBV study group (* the mean difference is significant at the .05 level). Adjusted for multiple comparisons: Bonferroni.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline vs treatment end</th>
<th>Treatment end vs 3-month follow-up</th>
<th>3-month follow-up vs baseline</th>
<th>SE</th>
<th>F- statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>.932*</td>
<td>.09</td>
<td>-.825*</td>
<td>.08</td>
<td>.107*</td>
</tr>
<tr>
<td>FSS</td>
<td>-1.440*</td>
<td>.38</td>
<td>.512*</td>
<td>.16</td>
<td>-.929*</td>
</tr>
<tr>
<td>PSQI</td>
<td>-3.059*</td>
<td>.63</td>
<td>2.499*</td>
<td>.47</td>
<td>-.569*</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>-14.644*</td>
<td>3.33</td>
<td>12.478*</td>
<td>1.76</td>
<td>-1.896*</td>
</tr>
<tr>
<td>POMS (Depression/Dejection scale)</td>
<td>-3.744*</td>
<td>1.07</td>
<td>4.292*</td>
<td>.48</td>
<td>.548</td>
</tr>
<tr>
<td>POMS (Anger/Hostility scale)</td>
<td>-2.249*</td>
<td>1.34</td>
<td>2.889*</td>
<td>.45</td>
<td>.640*</td>
</tr>
<tr>
<td>POMS (Confusion/Bewilderment scale)</td>
<td>-1.159*</td>
<td>.74</td>
<td>-.175</td>
<td>.48</td>
<td>-.964*</td>
</tr>
<tr>
<td>POMS (Fatigue/Inertia scale)</td>
<td>-2.212*</td>
<td>.04</td>
<td>.924*</td>
<td>.19</td>
<td>-1.288*</td>
</tr>
<tr>
<td>POMS (Tension/Anxiety scale)</td>
<td>-1.803*</td>
<td>.61</td>
<td>2.535*</td>
<td>.70</td>
<td>.732</td>
</tr>
<tr>
<td>POMS (Vigour/Activity scale)</td>
<td>3.520*</td>
<td>.76</td>
<td>-1.868*</td>
<td>.54</td>
<td>1.652*</td>
</tr>
<tr>
<td>HADS (Depression scale)</td>
<td>-1.720*</td>
<td>.40</td>
<td>1.880*</td>
<td>.36</td>
<td>.160</td>
</tr>
<tr>
<td>HADS (Anxiety scale)</td>
<td>-1.800*</td>
<td>.44</td>
<td>1.760*</td>
<td>.36</td>
<td>-.040</td>
</tr>
</tbody>
</table>
Table 6.10 (cont'd). Mean differences in baseline, treatment end and 3-month follow-up (adjusted means) for PEG IFN + RBV study group (* the mean difference is significant at the .05 level). Adjusted for multiple comparisons: Bonferroni.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline vs treatment end</th>
<th>Treatment end vs 3-month follow-up</th>
<th>3-month follow-up vs baseline</th>
<th>SE</th>
<th>F-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-R</td>
<td>1.480* .44</td>
<td>-1.920* .46</td>
<td>.440 .43</td>
<td></td>
<td>F (2.48) = 10.40, p &lt; .001</td>
</tr>
<tr>
<td>TMT (Part A)</td>
<td>.900 .51</td>
<td>1.560 .79</td>
<td>1.560* .74</td>
<td></td>
<td>F (2.48) = 3.39, p &lt; .05</td>
</tr>
<tr>
<td>TMT (Part B)</td>
<td>-3.920 1.69</td>
<td>8.760* 1.57</td>
<td>4.840* 1.07</td>
<td></td>
<td>F (1.62, 38.99) = 17.83, p &lt; .001</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>-.400 .94</td>
<td>-2.160 1.25</td>
<td>-2.560 1.37</td>
<td></td>
<td>F (2.48) = 42.41, p = .082</td>
</tr>
</tbody>
</table>
Table 6.11. *Patient reported measures adjusted means (standard deviations) for the triple therapy (Study 2) at baseline, treatment end and 3-month follow-up.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (SD) N =35</th>
<th>Treatment end Mean (SD) N =27</th>
<th>3-month follow-up Mean (SD) N =27</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUALITY OF LIFE INVENTORY (QOLI) (Range -6 to 6)</td>
<td>2.06(1.47)</td>
<td>1.08(0.84)</td>
<td>1.87(2.15)</td>
</tr>
<tr>
<td>FATIGUE SEVERITY SCALE (FSS) (Range 1-7)</td>
<td>4.74(1.79)</td>
<td>5.89(2.03)</td>
<td>5.26(2.19)</td>
</tr>
<tr>
<td>PITTSBURGH SLEEP QUALITY INDEX (PSQI) (Range 0-21)</td>
<td>7.89(3.34)</td>
<td>11.56(4.86)</td>
<td>8.67(3.09)</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES (POMS) (Range 0-168)</td>
<td>46.20(24.97)</td>
<td>57.65(27.10)</td>
<td>46.56(23.52)</td>
</tr>
<tr>
<td>Depression/Dejection scale</td>
<td>16.96(6.98)</td>
<td>15.65(7.11)</td>
<td>16.00(7.46)</td>
</tr>
<tr>
<td>Anger/Hostility scale</td>
<td>8.49(3.11)</td>
<td>10.22(3.80)</td>
<td>7.93(2.93)</td>
</tr>
<tr>
<td>Confusion/Bewilderment scale</td>
<td>9.04(3.47)</td>
<td>9.70(3.68)</td>
<td>9.48(3.38)</td>
</tr>
<tr>
<td>Fatigue/Inertia scale</td>
<td>11.17(4.85)</td>
<td>10.89(4.58)</td>
<td>11.52(5.12)</td>
</tr>
<tr>
<td>Tension/Anxiety scale</td>
<td>13.30(4.90)</td>
<td>12.63(4.87)</td>
<td>12.22(4.40)</td>
</tr>
<tr>
<td>Vigour/Activity scale</td>
<td>10.84(1.75)</td>
<td>10.82(1.64)</td>
<td>10.37(1.82)</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) DEPRESSION INDEX Range (0-21)</td>
<td>5.52(2.89)</td>
<td>5.56(2.08)</td>
<td>5.85(0.95)</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) ANXIETY INDEX Range (0-21)</td>
<td>6.26(1.86)</td>
<td>6.17(1.76)</td>
<td>6.22(1.48)</td>
</tr>
</tbody>
</table>
Table 6.11 (Cont’d). Patient reported measures adjusted means (standard deviations) for the triple therapy (Study 2) at baseline, treatment end and 3-month follow-up.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Treatment end</th>
<th>3-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) N=35</td>
<td>Mean (SD) N=27</td>
<td>Mean (SD) N=27</td>
</tr>
<tr>
<td>ADDENBROOKE’S COGNITIVE EXAMINATION REVISED (ACE-R)</td>
<td>93.04(3.90)</td>
<td>91.37(4.05)</td>
<td>94.19(2.42)</td>
</tr>
<tr>
<td>Range (0-100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAIL MAKING TEST PART A (TMT- PART A)</td>
<td>34.04(9.34)</td>
<td>36.37(6.43)</td>
<td>32.11(5.79)</td>
</tr>
<tr>
<td>Range (n/a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAIL MAKING TEST PART B (TMT- PART B)</td>
<td>82.74(24.98)</td>
<td>94.59(20.57)</td>
<td>79.15(15.04)</td>
</tr>
<tr>
<td>Range (n/a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18)</td>
<td>29.22(11.30)</td>
<td>32.85(14.37)</td>
<td>35.11(6.59)</td>
</tr>
<tr>
<td>Range (16-80)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6.12. Mean differences in baseline, treatment end and 3 month follow-up (adjusted means) for triple therapy study group (* the mean difference is significant at the .05 level). Adjusted for multiple comparisons: Bonferroni.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline vs treatment end</th>
<th>SE</th>
<th>Treatment end vs 3 month follow-up</th>
<th>SE</th>
<th>Baseline vs 3 month follow-up</th>
<th>SE</th>
<th>F- statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL1</td>
<td>.983*</td>
<td>.14</td>
<td>- .785*</td>
<td>.37</td>
<td>.198*</td>
<td>.04</td>
<td>F (1.19, 32.15) = 5.05, p &lt; .05</td>
</tr>
<tr>
<td>FSS</td>
<td>-1.148*</td>
<td>.16</td>
<td>0.630*</td>
<td>.15</td>
<td>- .519*</td>
<td>.17</td>
<td>F (2.52) = 5.58, p &lt; .001</td>
</tr>
<tr>
<td>PSQI</td>
<td>-3.667*</td>
<td>.39</td>
<td>2.889*</td>
<td>.60</td>
<td>- .778*</td>
<td>.42</td>
<td>F (1.52, 39.42) = 32.66, p &lt; .001</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>-11.450*</td>
<td>1.42</td>
<td>11.094*</td>
<td>.80</td>
<td>.365</td>
<td>1.15</td>
<td>F (1.48, 38.44) = 63.17, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Depression/Dejection scale)</td>
<td>-2.311*</td>
<td>.78</td>
<td>3.000*</td>
<td>.26</td>
<td>.689</td>
<td>.70</td>
<td>F (1.16, 30.17) = 12.73, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Anger/Hostility scale)</td>
<td>-1.731*</td>
<td>.16</td>
<td>2.296*</td>
<td>.21</td>
<td>.565*</td>
<td>.08</td>
<td>F (1.13, 29.35) = 111.35, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Confusion/Bewilderment scale)</td>
<td>-0.667*</td>
<td>.12</td>
<td>.222*</td>
<td>.13</td>
<td>-.444</td>
<td>.10</td>
<td>F (2.52) = 16.55, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Fatigue/Inertia scale)</td>
<td>-1.770*</td>
<td>.17</td>
<td>1.426*</td>
<td>.17</td>
<td>-.344*</td>
<td>.12</td>
<td>F (2.52) = 25.00, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Tension/Anxiety scale)</td>
<td>-0.937*</td>
<td>.10</td>
<td>1.481*</td>
<td>.20</td>
<td>1.084*</td>
<td>.14</td>
<td>F (1.30, 38.83) = 52.22, p &lt; .001</td>
</tr>
<tr>
<td>POMS (Vigour/Activity scale)</td>
<td>2.919*</td>
<td>.09</td>
<td>-2.447*</td>
<td>.19</td>
<td>.473*</td>
<td>.18</td>
<td>F (1.58, 35.68) = 193.48, p &lt; .001</td>
</tr>
<tr>
<td>HADS (Depression scale)</td>
<td>-2.057*</td>
<td>.43</td>
<td>1.704*</td>
<td>.62</td>
<td>.778</td>
<td>.45</td>
<td>F (1.62, 42.10) = 12.63, p &lt; .001</td>
</tr>
<tr>
<td>HADS (Anxiety scale)</td>
<td>-1.926*</td>
<td>.48</td>
<td>1.963*</td>
<td>.20</td>
<td>.037</td>
<td>.34</td>
<td>F (1.51, 39.25) = 28.28, p &lt; .001</td>
</tr>
</tbody>
</table>
Table 6.12 (cont'd). Mean differences in baseline, treatment end and 3 month follow-up (adjusted means) for triple therapy study group (* the mean difference is significant at the .05 level). Adjusted for multiple comparisons: Bonferroni.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline vs treatment end</th>
<th>SE</th>
<th>Treatment end vs 3 month follow-up</th>
<th>SE</th>
<th>3-month follow-up vs baseline</th>
<th>SE</th>
<th>F- statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-R</td>
<td>1.667*</td>
<td>.48</td>
<td>-2.815*</td>
<td>.66</td>
<td>-1.148</td>
<td>.69</td>
<td>F (2.52) = 10.55, p &lt; .001</td>
</tr>
<tr>
<td>TMT (Part A)</td>
<td>-2.333</td>
<td>1.33</td>
<td>4.259*</td>
<td>1.28</td>
<td>1.926</td>
<td>2.06</td>
<td>F (1.38, 35.81) = 25.60, p &lt; .001</td>
</tr>
<tr>
<td>TMT (Part B)</td>
<td>-11.852*</td>
<td>2.99</td>
<td>15.444*</td>
<td>5.27</td>
<td>3.593</td>
<td>6.02</td>
<td>F (1.39, 36.06) = 5.37, p &lt; .05</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>-3.630</td>
<td>3.31</td>
<td>-2.259</td>
<td>2.72</td>
<td>-5.889</td>
<td>2.72</td>
<td>F (2.52) = 1.79, p = .123</td>
</tr>
</tbody>
</table>
6.6.1 QUALITY OF LIFE (QOL)

On average PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end reported significantly less QOL than they reported at baseline (treatment end: $M = 1.03, SD = .44$; baseline: $M = 1.96, SD = .72$, $p < .001$ and treatment end: $M = 1.08, SD = .84$; baseline: $M = 2.06, SD = 1.47$, $p < .001$) respectively. Also, on average patients at 3-month follow-up to treatment end reported significantly better QOL than they reported at treatment end (3-month follow-up: $M = 1.85, SD = .67$; treatment end: $M = 1.03, SD = .44$, $p < .05$ and 3-month follow-up: $M = 1.87, SD = 2.15$; treatment end: $M = 1.08, SD = .84$, $p < .05$) respectively.

Furthermore, analysis of the data at three-month follow-up indicates that patients in the PEG IFN + RBV (Study 1) and triple therapy (Study 2) had mean QOL scores that did not return to baseline (pre-treatment) levels, suggesting ongoing poorer QOL at 3-month post treatment follow-up (baseline: $M = 1.96, SD = .72$; 3-month follow-up: $M = 1.85, SD = .67$, $p$...
< .05 and baseline: $M = 2.06, SD = 1.47$; 3-month follow-up: $M = 1.87, SD = 2.15, p < .05)$ respectively (see Figures 6.7 and 6.8).

The QOLI overall mean score is a product of the importance ratings and satisfaction ratings (Frisch, 1994). Any changes in the QOLI overall mean score can be a result of changes in the relative satisfaction and importance ratings. To examine the contribution of satisfaction ratings and importance ratings to the QOLI overall mean score (i.e. the product of satisfaction ratings x importance ratings) the correlation between satisfaction ratings and the importance ratings, and the QOLI overall mean score were calculated for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

The correlations across PEG IFN + RBV (Study 1) and triple therapy (Study 2) at baseline between the satisfaction ratings and the QOLI overall mean score were $r = 0.77$ and $r = .79$ respectively. The median correlations between the importance ratings and the QOLI mean scores at baseline were $r = 0.27$ and $r = .20$ respectively. Furthermore, the correlations at treatment end between satisfaction ratings and the QOLI overall mean scores were $r = 0.80$ and $r =0.81$ respectively and between importance rating and the QOLI overall mean scores were $r = 0.15$ and $r =0.14$ respectively. In addition, at three-month follow-up the correlations between satisfaction ratings and QOLI overall mean scores were $r = 0.76$ and $r = 0.78$ respectively and the between importance ratings and QOLI overall mean scores were $r = 0.18$ and $r = 0.22$ respectively. These correlations suggest that for most patients the QOLI overall mean scores at patients in both studies at baseline, treatment end and three-month follow-up were primarily a function of satisfaction.

**QOLI domains**

The overall mean scores and standard deviations of the 16 domains of the QOLI at baseline, treatment end and three-month follow-up for PEG IFN + RBV (Study 1) and triple therapy (Study 2) are given in Tables 6.13 and 6.14. The satisfaction and importance ratings
mean scores and standard deviations of the 16 domains of the QOLI at baseline, treatment end and three-month follow-up for PEG IFN + RBV (Study 1) and triple therapy (Study 2) are given in Appendix Tables N.3, N.4, N.5 and N.6. The means presented in these Tables are unadjusted means. Statistical significance of the pairwise differences was based on a repeated measures analysis of variance model to account for the within-subject correlation of each domain of the QOLI.

For both PEG IFN + RBV (Study 1) and triple therapy (Study 2) the following domains showed no significant satisfaction ratings changes between any of the three time points: Money, Work, Children, Relatives, Home, Neighbourhood and Community. For both studies the satisfaction ratings that changed the most, in relation to the other domains, between baseline and treatment end, were Health, Play, Creativity, and Goals. These domains would have a relatively greater influence on the change in the QOLI overall mean scores between baseline and treatment end than other domains. In all cases the changes in those four domains were significant ($p < .05$). For both studies for the satisfaction ratings there was a significant change in mean scores from treatment end to three-month follow-up in 10 of the 16 domains. Furthermore, the domains of the QOLI satisfaction ratings that changed the most relative to other domains between treatment end and three-month follow-up were: Health, Self-esteem, Goals, Play and Helping (see Appendix Tables N.3 and N.4).

The domains Goals, Play, Learning, Creativity, and Love showed a significant decrease in satisfaction ratings at three-month follow-up compared to baseline. The domain Self-esteem showed an improvement in satisfaction ratings at three-month follow-up compared to baseline for both studies but the difference was not significant.
Table 6.13. QOLI overall mean (Standard Deviation) for individual domains at baseline, treatment end and three-month follow-up for PEG IFN + RBV (Study 1).

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline M (SD) N = 30</th>
<th>Treatment end M(SD) N= 26</th>
<th>Three-month follow-up M(SD) N= 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>1.15(1.16)</td>
<td>-1.85(3.11)(^a)</td>
<td>1.19(3.46)(^b)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.10(1.30)</td>
<td>0.42(2.84)(^a)</td>
<td>1.05(2.35)(^b)</td>
</tr>
<tr>
<td>Goals</td>
<td>2.23(0.97)</td>
<td>1.00(2.32)(^a)</td>
<td>1.90(1.98)(^b,c)</td>
</tr>
<tr>
<td>Money</td>
<td>0.93(1.91)</td>
<td>0.86(1.95)</td>
<td>0.90(1.75)</td>
</tr>
<tr>
<td>Work</td>
<td>1.03(1.99)</td>
<td>0.90(2.12)</td>
<td>1.07(1.74)</td>
</tr>
<tr>
<td>Play</td>
<td>2.23(1.63)</td>
<td>-0.27(2.49)(^a)</td>
<td>1.96(2.33)(^b,c)</td>
</tr>
<tr>
<td>Learning</td>
<td>1.67(0.92)</td>
<td>1.00(2.37)(^a)</td>
<td>1.50(2.08)(^b)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.57(1.17)</td>
<td>0.80(2.48)(^a)</td>
<td>1.20(2.29)(^b,c)</td>
</tr>
<tr>
<td>Helping</td>
<td>1.17(1.18)</td>
<td>0.50(2.37)(^a)</td>
<td>1.15(1.96)(^b)</td>
</tr>
<tr>
<td>Love</td>
<td>1.40(1.82)</td>
<td>0.80(2.24)(^a)</td>
<td>1.06(2.23)(^b,c)</td>
</tr>
<tr>
<td>Friends</td>
<td>1.47(2.27)</td>
<td>1.00(1.60)(^a)</td>
<td>1.20(2.31)(^b)</td>
</tr>
<tr>
<td>Children</td>
<td>0.73(3.26)</td>
<td>0.70(2.68)</td>
<td>0.75(2.15)</td>
</tr>
<tr>
<td>Relatives</td>
<td>2.27(2.11)</td>
<td>2.46(2.08)</td>
<td>2.40(2.48)</td>
</tr>
<tr>
<td>Home</td>
<td>1.19(2.45)</td>
<td>1.18(1.98)</td>
<td>1.25(2.55)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.37(1.94)</td>
<td>1.30(1.46)</td>
<td>1.35(1.42)</td>
</tr>
<tr>
<td>Community</td>
<td>1.76(1.25)</td>
<td>1.60(2.66)</td>
<td>1.75(1.58)</td>
</tr>
</tbody>
</table>

The mean changes which are significant (p <.05) are identified by the following subscripts

\(^a\) = significant difference between treatment end and baseline

\(^b\) = significant difference between three-month follow-up and treatment end

\(^c\) = significant difference between three-month follow-up and baseline.
Table 6.14. *Overall QOLI mean (Standard Deviation) in individual domains at baseline, treatment end and three-month follow-up for triple therapy (Study 2)*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline Mean (SD)</th>
<th>Treatment end Mean (SD)</th>
<th>Three-month follow-up Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 35</td>
<td>N = 27</td>
<td>N = 27</td>
</tr>
<tr>
<td>Health</td>
<td>1.12(1.29)</td>
<td>-1.44(2.52)</td>
<td>1.13(1.25)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.22(1.20)</td>
<td>0.37(2.33)</td>
<td>1.21(1.15)</td>
</tr>
<tr>
<td>Goals</td>
<td>2.23(0.97)</td>
<td>0.80(1.92)</td>
<td>2.05(1.05)</td>
</tr>
<tr>
<td>Money</td>
<td>0.90(1.46)</td>
<td>0.85(1.93)</td>
<td>0.90(1.72)</td>
</tr>
<tr>
<td>Work</td>
<td>1.11(2.52)</td>
<td>0.78(2.00)</td>
<td>1.13(2.02)</td>
</tr>
<tr>
<td>Play</td>
<td>1.63(2.00)</td>
<td>-0.15(2.57)</td>
<td>1.54(2.07)</td>
</tr>
<tr>
<td>Learning</td>
<td>1.77(1.46)</td>
<td>0.85(1.99)</td>
<td>1.67(1.58)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.79(1.23)</td>
<td>0.73(2.18)</td>
<td>1.56(1.35)</td>
</tr>
<tr>
<td>Helping</td>
<td>1.51(1.79)</td>
<td>0.51(2.17)</td>
<td>1.50(1.99)</td>
</tr>
<tr>
<td>Love</td>
<td>1.30(2.40)</td>
<td>0.66(1.85)</td>
<td>1.00(2.65)</td>
</tr>
<tr>
<td>Friends</td>
<td>1.49(2.37)</td>
<td>1.00(1.66)</td>
<td>1.12(2.15)</td>
</tr>
<tr>
<td>Children</td>
<td>0.88(2.95)</td>
<td>0.84(2.61)</td>
<td>0.88(2.58)</td>
</tr>
<tr>
<td>Relatives</td>
<td>2.00(2.58)</td>
<td>2.20(1.97)</td>
<td>2.35(2.32)</td>
</tr>
<tr>
<td>Home</td>
<td>1.23(2.49)</td>
<td>1.22(1.94)</td>
<td>1.26(2.93)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.25(2.51)</td>
<td>1.18(1.40)</td>
<td>1.23(1.49)</td>
</tr>
<tr>
<td>Community</td>
<td>1.54(1.01)</td>
<td>1.40(1.96)</td>
<td>1.52(1.28)</td>
</tr>
</tbody>
</table>

The mean changes which are significant (p < .05) are identified by the following subscripts:

- **a** = significant difference between treatment end and baseline
- **b** = significant difference between three-month follow-up and treatment end
- **c** = significant difference between three-month follow-up and baseline
The domain Health showed an improved satisfaction rating at three-month follow-up compared to baseline (three-month follow-up: $M = 0.76, SD = 0.45$), baseline: $M = 0.70, SD = 0.45$) for PEG IFN + RBV (Study 1) but showed an impairment at three-month follow-up compared to baseline (three-month follow-up: $M = 0.70 (SD = 0.40)$, baseline: $M = 0.72 (SD = 0.49)$) for triple therapy (Study 2). In both cases the differences were not significant.

The importance ratings for PEG IFN + RBV (Study 1) and triple therapy (Study 2) were investigated to determine the QOLI domains that patients reported as having relatively higher importance ratings and relatively lower satisfaction ratings compared to the other QOLI domains. At baseline four domains showed relatively higher importance ratings for both the PEG IFN + RBV (Study 1) and triple therapy (Study 2): Friends ($M = 1.67 (SD = 1.27)$), $M = 1.69 (SD = 1.56)$), Goals ($M = 1.57 (SD = 0.97)$), $M = 1.57 (SD = 0.89)$), Self-esteem ($M = 1.53 (SD = 1.30)$), $M = 1.63 (SD = 1.13)$, and Health ($M = 1.50 (SD = 1.16)$), $M = 1.60 (SD = 1.04)$ respectively. In addition, for PEG IFN + RBV (Study 1) the domain Relatives ($M = 1.50, SD = 1.11$)) was also relatively higher and for triple therapy (Study 2) the domain Play ($M = 1.66(SD = 1.53)$) was also relatively higher. All six of these QOLI domains continued to show relatively higher importance ratings at treatment end and at three-month follow-up.

The domain Friends showed a relatively high importance rating at all three time points for both PEG IFN + RBV (Study 1) and triple therapy (Study 2) studies. For both studies at treatment end the domain showed a relatively high importance rating and a relatively low satisfaction rating: (importance ratings: $M = 1.67$, $M = 1.60$, satisfaction ratings $M = 0.75$, $M = 0.65$) respectively. However, at three-month follow-up importance ratings were still relatively high but the satisfaction ratings had improved: (importance ratings: $M = 1.60$, $M = 1.62$, satisfaction ratings $M = 1.15$, $M = 1.27$).
The domain Goals also showed a relatively high importance rating at all three time points for both PEG IFN + RBV (Study 1) and triple therapy (Study 2), however at treatment end the domain showed a relatively low satisfaction rating: (importance ratings: $M = 1.23$, $M = 1.23$, satisfaction ratings $M = 0.62$, $M = 0.54$) respectively. At three-month follow-up satisfaction ratings improved compared to treatment end (three-month follow-up: $M = 1.24$, $M = 1.45$; treatment end $M = 0.62$, $M = 0.54$) respectively but were still below baseline satisfaction ratings ($M = 1.47$, $M = 1.60$) respectively.

Two domains showed relatively lower satisfaction ratings at baseline and higher importance ratings at baseline for PEG IFN + RBV (Study 1) and triple therapy (Study 2): Self-esteem (satisfaction ratings: $M = 0.66$, $M = 0.70$; importance ratings $M = 1.53$, $M = 1.63$), respectively, and Health (satisfaction ratings: $M = 0.70$, $M = 0.72$, importance ratings $M = 1.50$, $M = 1.60$) respectively. This was also the case at treatment end: Self-esteem (satisfaction ratings: $M = 0.26$, $M = 0.24$; importance ratings $M = 1.73$, $M = 1.80$), respectively, and Health (satisfaction ratings: $M = -1.23$, $M = -1.01$, importance ratings $M = 1.73$, $M = 1.84$) respectively. At three-month follow-up the domain Self-esteem showed improved, but still relatively low, satisfaction rating and a high importance rating (satisfaction ratings: $M = 0.70$, $M = 0.75$; importance ratings $M = 1.96$, $M = 1.94$), respectively. The domain Health also continued to show a relatively low, although improved, satisfaction rating and a relatively high importance rating (satisfaction ratings: $M = 0.76$, $M = 0.70$, importance ratings $M = 1.84$, $M = 1.96$) respectively.

In the PEG IFN + RBV (Study 1), the other domain with a relatively higher importance rating was Relatives. This domain showed a relatively higher importance rating at treatment end and a relatively lower satisfaction rating at treatment end (importance rating, $M = 1.50$; satisfaction rating, $M = -0.05$). However, the satisfaction rating improved at three-month follow-up (importance rating $M = 1.50$, satisfaction rating $M = 1.75$).
For the triple therapy (Study 2) the domain Play had a relatively high importance rating ($M = 1.46$) at the one time point treatment end. At that time point the satisfaction rating was relatively low ($M = -0.05$), compared to baseline (importance rating: $M = 1.66$, satisfaction rating: $M = 1.06$) and three-month follow-up (importance rating: $M = 1.64$, satisfaction rating: $M = 1.03$).

The five domains Money, Children, Love, Work and Helping showed relatively the lowest importance ratings for both studies and across the three-time points baseline, treatment end and three-month follow-up.

**6.6.2 FATIGUE AND SLEEP DISORDERS**

For both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end, on average, reported a mean score of 5.76 ($SD = 1.29$) and 5.89 ($SD = 2.03$) respectively and these mean scores were significant increases from the FSS baseline mean scores of 4.32 ($SD = 1.82$, $p < .001$) and 4.74 ($SD = 1.79$, $p < .001$) respectively. Furthermore, for PEG IFN + RBV (Study 1) and triple therapy (Study 2) at three-month follow-up to treatment end, patients on average reported a FSS mean scores of 5.25 ($SD = 1.28$) and 5.26 ($SD = 2.19$) respectively, which were significantly less than the treatment end mean scores of 5.76 ($SD = 1.29$, $p < .05$), and 5.89 ($SD = 2.03$, $p < .001$) respectively, and were also
significantly higher than the reported mean scores at baseline $M = 4.32$, $(SD = 1.82, p < .001)$ and $M = 4.74$, $(SD = 1.79, p < .05)$ respectively (see Tables 6.10 and 6.12 and Figures 6.9 and 6.10). Analyses indicate that a change of 0.33-0.82 in mean FSS scores represents a meaningful change in fatigue (Rosa et al., 2014).

Fatigue was also measured by the POMS Fatigue/Inertia scale (see Tables 6.10 and 6.12 and Figures 6.21 and 6.22). The results of the POMS Fatigue/Inertia scale showed similar trends between the three time periods as reported by the FSS measure. On average patients in the PEG IFN + RBV (Study 1) and triple therapy (Study 2) reported significantly more fatigue and inertia at treatment end than they reported at baseline (treatment end: $M = 12.93$, $SD = 2.35$; baseline: $M = 10.52$, $SD = 4.12$, $p < .001$ and treatment end: $M = 12.94$, $SD = 5.64$; baseline: $M = 11.17$, $SD = 4.85$, $p < .001$) respectively. Also, on average, patients at three-month follow-up to treatment end patients reported significantly less fatigue and inertia than they reported at treatment end (3-month follow-up: $M = 12.01$, $SD = 2.93$; treatment end: $M = 12.93$, $SD = 2.35$, $p < .05$ and three-month follow-up: $M = 11.52$, $SD = 5.12$; treatment end: $M = 12.94$, $SD = 5.64$, $p < .001$ respectively). However, for both the FSS and the POMS Fatigue /Inertia scale and for both PEG IFN + RBV (Study 1) and triple
therapy (Study 2), patients were still reporting significantly more impaired fatigue at three-
months follow-up when compared to baseline (three-month follow-up: \( M = 12.01, SD = 2.93 \);
baseline: \( M = 10.52, SD = 4.12, p < .05 \) and three-month follow-up: \( M = 11.52, SD = 5.12 \);
baseline: \( M = 11.17, SD = 4.85, p < .001 \) respectively).

Patients also completed the POMS Vigour/Activity scale of the POMS measure. In
contrast to other POMS scales lower scores in this scale indicate an increase in impaired
psychological symptoms. On average, for the PEG IFN + RBV (Study 1) and triple therapy
(Study 2) patients at treatment end reported less vigour and activity than they reported at
baseline (treatment end: \( M = 8.12, SD = 1.67 \); baseline: \( M = 11.64, SD = 3.68, p < .001 \) and
treatment end: \( M = 7.92, SD = 1.28 \); baseline: \( M = 10.84, SD = 1.75, p < .001 \) respectively).

However, PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients reported
vigour and activity, at 3-month follow-up to treatment end, to be significantly increased \(( p
< .05)\) from that reported at treatment end (three-month follow-up: \( M = 9.99, SD = 2.36 \);
treatment end: \( M = 8.12, SD = 1.67, p < .05 \) and three-month follow-up: \( M = 10.37, SD =
1.82 \); treatment end: \( M = 7.92, SD = 1.28, p < .05 \) respectively). Furthermore, on average
patients reported significantly more vigour and activity at baseline than they reported at 3-
month follow-up (baseline: \( M = 11.64, SD = 3.68 \); three-month follow-up: \( M = 9.99, SD =
2.36, p < .05 \) and baseline: \( M = 10.84, SD = 1.75 \); three-month follow-up: \( M = 10.37, SD =
1.82, p < .05 \) respectively) (see Tables 6.10 and 6.12 and Figures 6.25 and 6.26). At all three
time points the patients in the studies reported overall on average a mean score for the POMS
Vigour/Activity scale below the pain patient population (see Figure 6.4).

The two measures FSS and POMS Fatigue/Inertia scale are the inverse to the POMS
Vigour/Activity scale. For the FSS and POMS Fatigue/Inertia scale measures, for both
studies, there is a significant increase from baseline to treatment end and a significant
decrease from treatment end to three-months follow-up. Also, there is a significant increase
in these two measures from baseline to three-month follow-up. Furthermore, the POMS scale of Vigour/Activity significantly decreased from baseline to treatment end and significantly improved from treatment end to three-month follow-up and showed a significant impairment at three-month follow-up compared to baseline (see Table 6.21).

Patient sleep problems (measured by the PSQI) showed a similar trend to the reporting of fatigue. At treatment end PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients on average reported mean scores of 10.82 ($SD = 3.02$) and 11.56 ($SD = 4.86$) respectively. These mean scores were a significant ($p < .05$) increase from baseline mean scores of 7.76 ($SD = 2.88$) and 7.89 ($SD = 3.34$) respectively. Furthermore, at three-month follow-up to treatment end patients on average reported mean scores of 8.32 ($SD = 2.14$) and 8.67 ($SD = 3.09$) respectively. The mean scores at three-month follow-up were significantly ($p < .05$) less than the mean scores at treatment end. Although the mean scores at three-month follow-up ($M = 8.32$, $SD = 2.14$) and ($M = 8.67$, $SD = 3.09$) respectively, were decreases from treatment end ($M = 10.82$, $SD = 3.02$) and ($M = 11.56$, $SD = 4.86$) respectively, they had not returned to baseline levels ($M = 7.76$, $SD = 2.88$ and $M = 7.89$, $SD = 3.34$) respectively.
For the PEG IFN + RBV (Study 1) the difference between the PSQI mean scores at three-month follow-up ($M=8.67$, $SD = 3.09$) and baseline ($M = 7.89$, $SD = 3.34$) was not significant (see Tables 6.12 and 6.21). However, for the triple therapy (Study 2) the difference between PSQI mean scores at 3-month follow-up ($M=8.67$, $SD = 3.09$) and baseline ($M = 7.89$, $SD = 3.34$) was significant ($p<.05$) (see Tables 6.12 and 6.15).

For both studies patients on average reported a significant increase in sleep problems from baseline to treatment end but also reported on average a significant decrease in the level of sleep problems from treatment end to three-month follow-up. For the PEG IFN + RBV (Study 1) sleep was more impaired at three-month follow-up compared to baseline but the difference was not significant. For the triple therapy (Study 2) at three-month follow-up sleep was significantly impaired compared to baseline ($p <.05$) (see Tables 6.10 and 6.13).

Table 6.15. *Summary of relationship between three-month follow-up mean and baseline mean for PEG IFN + RBV (Study 1) and triple therapy (Study 2) for fatigue and sleep measures.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Relationship 3-month follow-up mean to baseline mean</th>
<th>$p$ -value</th>
</tr>
</thead>
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<tr>
<td>PEG IFN + RBV (Study 1)</td>
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<td>FSS</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>PSQI</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>Triple therapy (Study 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>PSQI</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

ns = not significant
A summary of the differences in fatigue and sleep mean scores between baseline and three-month follow-up for the two studies is presented in Table 6.11. The significant impairment of fatigue and sleep compared to baseline in both studies indicates ongoing problems with these two psychological symptoms three-months following the end of treatment.

6.6.3 **MOOD DISTURBANCE**

The Total Mood Disturbance (TMD) for this study was measured using the Profile of Mood States (POMS). The TMD is calculated as the sum of the 5 scales Depression/Dejection, Anger/Hostility, Confusion/Bewilderment, Fatigue/Inertia, and Tension/Anxiety minus the sixth scale Vigour/Activity. A higher mean score indicates greater mood disturbance.

From baseline to treatment end PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients reported a significant increase in TMD mean score (baseline: \( M = 44.12, SD = 20.35 \); treatment end: \( M = 58.76, SD = 14.35, p < .001 \) and baseline: \( M = 46.20, SD = 24.97 \); treatment end: \( M = 57.65, SD = 27.10, p < .001 \) respectively. From treatment end to three-month follow-up patients reported a significant decrease in the TMD score (treatment end: \( M = 58.76, SD = 14.35 \); three-month follow-up \( M = 46.02, SD = 14.98, p < .001 \) and treatment end: \( M = 57.76, SD = 24.97 \); three-month follow up: \( M = 46.56, SD = 23.52, p < .001 \) respectively. Furthermore, compared to baseline the three-month follow-up TMD scores reported were still higher (but not significantly) than at baseline (three-month follow-up \( M = 46.02, SD = 14.98 \), baseline: \( M = 44.12, SD = 20.35 \) and three-month follow-up \( M = 46.56, SD = 23.52, \) baseline: \( M = 46.20, SD = 24.97 \) respectively (see Table 6.10 and 6.12 and Figures 6.13 and 6.14).
The Fatigue/Inertia, and Vigour/Activity scales are discussed under section 6.6.2 Fatigue and Sleep Disorders (see page 202). The Depression/Dejection, and Tension/Anxiety scales are discussed under section 6.6.4 Depression and Anxiety (see page 213).

**POMS Anger/Hostility Scale**

On average PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end reported significantly more anger and hostility than they reported at baseline (treatment end: $M = 10.57$, $SD = 2.67$, baseline: $M = 8.32$, $SD = 1.03$, $p < .001$ and treatment end: $M = 10.22$, $SD = 3.80$, baseline: $M = 8.49$, $SD = 3.11$, $p < .001$) respectively.

Furthermore, at three-month follow-up patients reported significantly less anger and hostility than they reported at treatment end (three-month follow-up: $M = 7.68$, $SD = 0.49$, treatment end: $M = 10.57$, $SD = 2.67$, $p < .001$ and three-month follow-up: $M = 7.93$, $SD = 2.93$, treatment end: $M = 10.22$, $SD = 3.80$, $p < .001$) respectively. Finally, at three-month follow-up patients reported significantly less anger and hostility than they reported at baseline (three-month follow-up: $M = 7.68$, $SD = 0.49$, baseline: $M = 8.32$, $SD = 1.03$, $p < .001$ and three-month follow-up: $M = 7.93$, $SD = 2.93$, baseline: $M = 8.49$, $SD = 3.11$, $p < .001$) respectively (see Tables 6.10 and 6.12 and Figures 6.13 and 6.14).
At both baseline and 3-month follow-up the mean scores reported by patients in both studies were higher than for the mean scores for healthy older adults ($M = 4.70$). Also, for both studies, at baseline the mean scores were higher than the pain patient population control mean score ($M = 8.00$), and the Anger/Hostility scale mean scores reported by patients at three-month follow-up neared the pain patient population control score of 8.00 (see Figure 6.6).

**POMS Confusion/Bewilderment Scale**

GLM repeated measures determined that the Confusion/Hostility Scale did not differ significantly between any time points ($F(2.48) = 1.89, p = .162$). At all time points patients in the PEG IFN + RBV therapy study reported an overall mean score above the 7.32 mean score for the pain patient population (see Appendix Table N.1 and Figures 6.6 and 6.19).
Figure 6.15. Changes in POMS Depression/Dejection Scale

Figure 6.16. Changes in POMS Depression/Dejection Scale

Figure 6.17. Changes in POMS Anger/Hostility Scale

Figure 6.18. Changes in POMS Anger/Hostility Scale

Figure 6.19. Changes in POMS Confusion/Bewilderment Scale

Figure 6.20. Changes in POMS Confusion/Bewilderment Scale
Figure 6.21. Changes in POMS Fatigue/Inertia Scale

Figure 6.22. Changes in POMS Fatigue/Inertia Scale

Figure 6.23. Changes in POMS Tension/Anxiety Scale

Figure 6.24. Changes in POMS Tension/Anxiety Scale

Figure 6.25. Changes in POMS Vigour/Activity Scale

Figure 6.26. Changes in POMS Vigour/Activity Scale
For the triple therapy (Study 2), on average patients at treatment end reported significantly more confusion and bewilderment than they reported at baseline (treatment end: $M = 9.70, SD = 3.68$; baseline: $M = 9.04, SD = 3.47, p < .001$). At three-month follow-up patients reported less confusion and bewilderment than they reported at treatment end (three-month follow-up: $M = 9.48, SD = 3.38$; treatment end: $M = 9.70, SD = 3.68$) but the difference was not significant. Patients reported less confusion and bewilderment at baseline than they reported at three-month follow-up (baseline: $M = 9.04, SD = 3.47$; 3-month follow-up: $M = 9.48, SD = 3.38$), but the difference was not significant (see Table 6.14 and Figure 6.20). The baseline mean score (9.07) and three-month follow-up mean score (9.48) were above the normal mean score recorded for pain patient’s population (see Figures 6.6).

6.6.4 DEPRESSION AND ANXIETY

Depression

On average patients for PEG IFN + RBV (Study 1) and triple therapy (Study 2) at treatment end reported on the HADS Depression scale significantly more symptoms of depression than at baseline (treatment end: $M = 7.28, SD = 1.77$; baseline: $M = 5.56, SD = 2.31, p < .001$) and treatment end: $M = 7.56, SD = 3.11$; baseline: $M = 5.52, SD = 2.89, p < .001$) respectively. Patients at three-month follow-up compared to treatment end reported significantly fewer symptoms of depression than at treatment end (three-month follow-up: $M = 5.40, SD = 1.35$; treatment end: $M = 7.28, SD = 1.77, p < .001$ and three-month follow-up: $M = 5.85, SD = 0.95$; treatment end: $M = 7.56, SD = 3.11, p < .001$) for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) respectively.

Although at baseline PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients reported more depression symptoms than at three-month follow-up the differences were not significant for both studies (baseline: $M = 5.56, SD = 2.31$; three-month follow-up: $M =$
5.40, SD = 1.35 and baseline: \( M = 5.52, SD = 2.89 \) and three-month follow-up: \( M = 5.85, SD = 0.95 \) respectively (see Tables 6.10 and 6.12 and Figures 6.27 and 6.28).

The trend reported and significance for the HADS Depression scale, for both studies for the three time points was the similar to the trend for the POMS Depression/Dejection scale with the exception that for triple therapy (Study 2) where the mean score at Three-months follow-up was less than the mean score at baseline. For the triple therapy (Study 2) the HADS depression scale mean score at three-months follow-up was more than the mean score at baseline. In both cases the difference between baseline and three-month follow-up was not significant (see Table 6.12 and Figures 6.16 and 6.28).

Using the POMS Depression/Dejection scale patients at treatment end reported on average significantly more depression and dejection than they reported at baseline for both PEG IFN + RBV (Study 1) and triple therapy (Study 2) (treatment end: \( M = 19.00, SD = 8.50 \); baseline: \( M = 15.88, SD = 6.11, p < .05 \) and (treatment end: \( M = 19.62, SD = 4.68 \); baseline: \( M = 16.96, SD = 6.98, p < .05 \) respectively. At 3-month follow-up to treatment end patients reported significantly less depression and dejection than they reported at treatment end (3-month follow-up: \( M = 15.33, SD = 3.79 \); treatment end: \( M = 19.00, SD = 8.50, p < .001 \) and 3-month follow-up: \( M = 16.00, SD = 7.46 \); treatment end: \( M = 19.62, SD = 4.68, p < .001 \) respectively. Furthermore, patients reported more depression and dejection at baseline than they reported at three-month follow-up but this difference was not significant (baseline: \( M = 15.88, SD = 6.11 \); three-month follow-up: \( M = 15.33, SD = 3.79 \) and baseline: \( M = 16.96, SD = 6.98 \); three-month follow-up: \( M = 16.00, SD = 7.46 \) respectively (see Tables 6.10 and 6.12 and Figures 6.15 and 6.16). Both the POMS Depression/Dejection scale baseline mean scores (15.88 and 16.96) and three-month follow-up mean scores (15.33 and 16.00), respectively, were above the POMS Depression/ Dejection scale normal mean score recorded for pain patient’s population (see Figure 6.6).
Anxiety

For the two studies the trend reported for the mean symptoms of anxiety on the HADS Anxiety scale was similar to that reported for depression scale except the anxiety mean score on the HADS, for the PEG IFN + RBV (Study 1) at three-month follow-up was higher than the anxiety mean score at baseline and for the triple therapy (Study 2) the anxiety mean score at three-month follow-up was less than the anxiety mean score at baseline. The differences, however, were not significant (see Figure 6.14).
On average PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end reported significantly more anxiety than at baseline (treatment end: $M = 8.16, SD = 2.10$; baseline: $M = 6.36, SD = 2.06, p < .05$ and treatment end: $M = 8.19, SD = 2.08$ baseline: $M = 6.26, SD = 1.86, p < .05$ respectively). In addition, patients at 3-month follow-up to treatment end reported significantly less anxiety than at treatment end (3-month follow-up: $M = 6.40, SD = 2.02$; treatment end: $M = 8.16, SD = 2.10, p < .001$ and 3-month follow-up: $M = 6.22, SD = 1.48$; treatment end: $M = 8.19, SD = 2.008, p < .001$ respectively).

Finally, patients reported less anxiety at baseline than at 3-month follow-up but this difference was not significant (baseline: $M = 6.36, SD = 2.10$; 3-month follow-up: $M = 6.40, SD = 2.02$ and baseline: $M = 6.26, SD = 1.86$; 3-month follow-up: $M = 6.22, SD = 1.48$) (see Table 6.6).

Patients completed the POMS measure which included the Tension/Anxiety Scale. For both studies the POMS Tension/Anxiety scale indicated a similar trend as the HADS Anxiety Scale excepting that for the triple therapy (Study 2) the difference between means between three-month follow-up and baseline for the POMS Tension/Anxiety scale was significant ($p < .001$), whereas for the HADS Anxiety scale the difference between means three-month follow-up and baseline was not significant (see Figures 6.23, 6.24,6.29 and 6.30).

On average for PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end reported significantly more tension and anxiety than they reported at baseline (treatment end: $M = 14.02, SD = 3.48$; baseline: $M = 12.22, SD = 4.09, p < .05$ and treatment end: $M = 13.70, SD = 5.25$; baseline: $M = 13.30, SD = 4.90, p < .05$ respectively). Also, on average patients at three-month follow-up to treatment end reported significantly less tension and anxiety than they reported at treatment end (three-month follow-up: $M = 11.49, SD = 3.63$; treatment end: $M = 14.02, SD = 3.49, p < .001$ and three-month follow-up: $M = 12.22,$
Furthermore, on average PEG IFN + RBV patients reported less tension and anxiety at 3-month follow-up than at baseline but the difference was not significant (three-month follow-up: $M = 11.49$, $SD = 3.63$, baseline $M = 12.22$, $SD = 4.09$; $p = 1.00$) (see Tables 6.12 and 6.22 and Figure 6.23). However, triple therapy (Study 2) patients on average reported less tension and anxiety at three-month follow-up than at baseline but the difference was significant (baseline: $M = 13.30$, $SD = 4.90$; three-month follow-up: $M = 12.22$, $SD = 4.40$, $p < .001$) (see Tables 6.12 and 6.16 and Figure 6.24). At all time points patients reported overall, on average, reported a mean score above older healthy adults ($M = 9.0$) and at treatment end reported, overall, on average, a mean score above the pain patient population ($M = 14.0$) (see Figure 6.6).

A summary of the differences between three-follow-up and baseline for the depression and anxiety measures is given in Table 6.16. This summary highlights that depression and anxiety return to baseline levels Three-months after the end of therapy. Also tension and anxiety as measured by the POMS Tension/Anxiety scale indicates patients reporting a significant improvement at three-month follow-up to treatment end compared to baseline.
Table 6.16. *Summary of relationship between three-month follow-up and baseline means for PEG IFN + RBV (Study 1) and triple therapy (Study 2) for depression and anxiety measures*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Relationship three-month follow-up mean to baseline mean</th>
<th><em>p</em>-value</th>
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<td></td>
<td></td>
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<tr>
<td>HADS Depression Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>3-month follow-up mean &gt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Triple therapy (Study 2)</strong></td>
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<td></td>
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<tr>
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</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>ns</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>3-month follow-up mean &lt; baseline mean</td>
<td>&lt;.001</td>
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</tbody>
</table>

ns= not significant

6.6.5 *COGNITIVE FUNCTIONING*

Cognitive functioning was measured using the ACE-R and TMT Trail Making Tests A and B. A higher score on the ACE-R indicates better cognitive functioning. Furthermore, a person who was more cognitively impaired would take longer to complete the TMT Trail Making Tests and therefore greater cognitive impairment would be recorded as a higher score denoted in seconds. The reported mean scores for the ACE-R test at baseline for PEG IFN + RBV (Study 1) and triple therapy (Study 2) were respectively $M = 93.92$ ($SD = 3.49$) and $M = 93.04$ ($SD = 3.90$), at treatment end $M = 92.44$ ($SD = 3.36$) and $M = 91.37$ ($SD = 4.05$) at 3-month follow-up $M = 94.36$ ($SD = 2.58$) and $M = 94.19$ ($SD = 2.42$). On average patients at treatment end had significantly lower cognitive function as measured by ACE-R than at
baseline ($p < .05; p < .001$) respectively and three-month follow-up ($p < .001; p < .05$) respectively. For both studies patients performed better on cognitive tests at three-month follow-up than at baseline, but these differences were not significant (Tables 6.12 and 6.14 and Figures 6.31 and 6.32).
The factors comprising the ACE-R are listed in Table 6.23. For both studies, at all three time points, the overall mean score for memory and verbal fluency was significantly less than the normative mean score for those factors. For PEG IFN + RBV (Study 1) and triple therapy (Study 2) the reported mean scores for the memory factor were at baseline 23.02 ($SD = 1.44$) and 23.01 ($SD = 1.46$), at treatment end 22.66 ($SD = 1.40$) and 22.60 ($SD = 1.38$), and at three-month follow-up 23.12 ($SD = 1.29$) and 23.29 ($SD = 1.41$) respectively. For both studies on average patients at treatment end had significantly lower memory mean scores than at baseline ($p < .05$) and three-month follow-up ($p < .001$) and patients performed better on cognitive tests for memory at three-month follow-up than at baseline, but the differences were not significant.

For PEG IFN + RBV (Study 1) and triple therapy (Study 2) the reported mean scores for the Verbal Fluency factor at baseline were; $M = 11.81$ ($SD = 2.67$), $M = 11.76$ ($SD = 2.67$) at treatment $M = 11.60$ ($SD = 2.51$), $M = 11.55$ ($SD = 2.52$) and at three-month follow-up $M = 11.89$ ($SD = 2.51$), $M = 11.91$ ($SD = 2.13$) respectively.

PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end had significantly lower memory mean scores than at baseline ($p < .05$) and three-month follow-up
Patients performed better on cognitive tests for memory at three-month follow-up than at baseline, but the differences were not significant (see Table 6.8).

For PEG IFN + RBV (Study 1) and triple therapy (Study 2) there were no significant change in patients’ TMT Part A scores between the three time points, baseline, treatment end, and three-month follow-up. However, at all three time points the patients in both studies took significantly longer \( (p < .05) \) than the normative mean (29 seconds) to complete Part A. (see Tables 6.10 and 6.12 and Figures 6.33 and 6.34).

The TMT Part A is relatively easier compared to Part B. PEG IFN + RBV (Study 1) patients took longer to complete the TMT Part B at treatment end than they did at baseline, but this did not differ significantly. Interestingly, for triple therapy (Study 2) patients took significantly longer to complete the TMT Part B at treatment end than they did at baseline (treatment end: \( M = 94.59, SD = 20.57; \) baseline: \( M = 82.74, SD = 24.98, p < .05 \) ) (see Tables 6.10 and 6.12 and Figures 6.35 and 6.36).

On average, PEG IFN + RBV (Study 1) patients at three-month follow-up to treatment end required significantly less time to complete the TMT Part B than they did at treatment end (three-month follow-up: \( M = 83.24, SD = 32.44; \) treatment end: \( M = 92.00, SD = 33.87, p < .001 \) ). Similarly, on average, triple therapy (Study 2) patients at three-month follow-up to treatment end required significantly less time to complete the TMT Trial B than they did at treatment end (3-month follow-up: \( M = 79.15, SD = 15.04; \) treatment end: \( M = 94.59, SD = 20.57, p < .05 \) ).

Also, on average, PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients at treatment end required significantly more time to complete the TMT Trial B than they did at baseline (baseline: \( M = 88.08, SD = 34.82.; \) treatment end: \( M = 92.00, SD = 33.87, p < .001 \) and baseline: \( M = 82.74, SD = 24.98.; \) treatment end: \( M = 94.59, SD = 20.57, p < .001 \) ) respectively. Furthermore, on average PEG IFN + RBV (Study 1) and triple therapy (Study
2) patients at three-month follow-up required significantly less time to complete the TMT Trial B than at baseline (three-month follow-up: $M = 83.24, SD = 32.44$; baseline: $M = 88.08, SD = 34.82$, $p < .001$ and three-month follow-up: $M = 94.19, SD = 20.57$; baseline: $M = 82.74, SD = 24.98$, $p < .001$) respectively (see Table 6.6 and Figure 6.16). Similarly, on average, triple therapy (Study 2) patients at three-month follow-up required significantly less time to complete the TMT Part B than they did at baseline (three-month follow-up: $M = 79.15, SD = 15.04$; baseline: $M = 82.74, SD = 24.98$, $p < .001$). The normative mean to complete the Trail B task is 79 seconds. At all three time points the patients in took longer than the normative mean to complete Part B.

6.6.6 PATIENT SATISFACTION

A higher mean score on the PSQ-18 indicates less patient satisfaction with medical treatment. Although, for both studies, there was an increase in reported patient treatment dissatisfaction on average at treatment end compared to baseline and at 3-month follow-up compared to treatment end the mean scores reported by patients did not differ significantly between any of the three time points. Furthermore, patients still reported at all time points a
level of treatment satisfaction higher than the normative population mean (see Tables 6.10 and 6.12 and Figures 6.37 and 6.38).

Table 6.17. ACE-R means (SD), at baseline, treatment end, three-month follow-up, and normative means (SD) for PEG IFN + RBV (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline Mean (SD)</th>
<th>Treatment end Mean (SD)</th>
<th>3-month follow-up Mean (SD)</th>
<th>Normative Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEG IFN + RBV (Study 1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/Orientation</td>
<td>17.99 (0.32)</td>
<td>17.90 (0.33)</td>
<td>18.00 (0.40)</td>
<td>17.60 (0.60)</td>
</tr>
<tr>
<td>Memory</td>
<td>23.02 (1.44)a</td>
<td>22.66 (1.40)a,b</td>
<td>23.12 (1.29)a,c</td>
<td>24.60 (1.20)</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>11.81 (2.67)a</td>
<td>11.60 (2.51)a,b</td>
<td>11.89 (2.15)a,c</td>
<td>12.60 (1.10)</td>
</tr>
<tr>
<td>Language</td>
<td>25.90 (0.27)</td>
<td>25.85 (0.30)</td>
<td>25.88 (0.40)</td>
<td>25.30 (0.90)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>15.24 (0.64)</td>
<td>15.20 (0.63)</td>
<td>15.35 (0.65)</td>
<td>15.50 (0.70)</td>
</tr>
<tr>
<td>Total ACE-R</td>
<td>93.92 (3.49)a</td>
<td>92.44 (3.36)a,b</td>
<td>94.36 (2.58)a,c</td>
<td>96.00 (2.70)</td>
</tr>
<tr>
<td><strong>Triple therapy (Study 2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/Orientation</td>
<td>17.89 (0.39)</td>
<td>17.87 (0.32)</td>
<td>17.90 (0.43)</td>
<td>17.60 (0.60)</td>
</tr>
<tr>
<td>Memory</td>
<td>23.01 (1.46)a</td>
<td>22.60 (1.38)a,b</td>
<td>23.29 (1.41)a,c</td>
<td>24.60 (1.20)</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>11.76 (2.67)a</td>
<td>11.55 (2.52)a,b</td>
<td>11.91 (2.13)a,c</td>
<td>12.60 (1.10)</td>
</tr>
<tr>
<td>Language</td>
<td>25.89 (0.28)</td>
<td>25.87 (0.32)</td>
<td>25.90 (0.42)</td>
<td>25.30 (0.90)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>15.23 (0.64)</td>
<td>15.21 (0.63)</td>
<td>15.33 (0.60)</td>
<td>15.50 (0.70)</td>
</tr>
<tr>
<td>Total ACE-R</td>
<td>93.04 (3.90)a</td>
<td>91.37 (4.05)a</td>
<td>94.19 (2.42)a,c</td>
<td>96.00 (2.70)</td>
</tr>
</tbody>
</table>

The significant differences ($p < .05$) are identified by the following subscripts:

a  Significant difference to normative mean score
b  Significant difference to baseline mean score
c  Significant difference to treatment end mean score
6.7 SECTION SEVEN
COMPARISON OF PEG IFN + RBV (STUDY 1) AND TRIPLE THERAPY (STUDY 2) OUTCOMES

Hypothesis 5.

The impairment of psychological symptoms will be significantly greater for triple therapy patients than for PEG IFN + RBV therapy at end of treatment, but there will be no significant difference at 3-month follow-up to treatment end.

The data from the GLM within subjects repeated measures for the 3 time points for the PEG IFN + RBV (Study 1) and the triple therapy (Study 2) are presented in Table 6.18.

The results of this analysis are plotted in Appendix Figures N.1 to N.16. Independent samples t-tests were conducted to determine whether there were any significant differences between the means of each therapy at treatment end and 3-month follow-up.

At baseline patients who were to undergo triple therapy reported significantly more tension and anxiety (p <.05) as measured by the POMS Tension/Anxiety scale than patients presenting for PEG IFN + RBV. In comparing patients who were to undergo triple therapy and PEG IFN + RBV therapy, there were no significant differences at baseline in the HADS Anxiety scale nor any of the other psychological symptoms measured in this study (see Table 6.24).

At the end of treatment patients who completed triple therapy reported significantly more impairment in sleep disorders (p <.001) as measured by the PSQI and tension and anxiety (p <.05) as measured by the POMS Tension/Anxiety scale, than patients who completed PEG IFN + RBV therapy. There were no other significant differences at treatment end for any other psychological symptoms measured in this study. Finally, at three-month follow-up the only significant differences between the two therapies reported by patients...
were in the POMS Tension/Anxiety ($p < .05$). Furthermore, for the other psychological symptoms measured there were no reported significant differences between the two therapies at three-month follow-up.

**Table 6.18.** Patient reported measures means (standard deviations) for the PEG IFN + RBV (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV Mean (SD)</th>
<th>Triple therapy Mean (SD)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUALITY OF LIFE INVENTORY (QOLI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range -6 to - 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.96(0.72)</td>
<td>2.06(1.47)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>1.03(0.44)</td>
<td>1.08(0.84)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>1.85(0.67)</td>
<td>1.87(2.15)</td>
<td>ns</td>
</tr>
<tr>
<td>FATIGUE SEVERITY SCALE (FSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 1-7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.32(1.82)</td>
<td>4.74(1.79)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>5.76(1.29)</td>
<td>5.89(2.03)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>5.25(1.28)</td>
<td>5.26(2.19)</td>
<td>ns</td>
</tr>
<tr>
<td>PITTSBURGH SLEEP QUALITY INDEX (PSQI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 0-21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.76(2.88)</td>
<td>7.89(3.34)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>10.82(3.02)</td>
<td>11.56(4.86)</td>
<td>.001</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>8.32(2.14)</td>
<td>8.67(3.09)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES (POMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 0-168)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44.12(20.35)</td>
<td>46.20(24.97)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>58.76(14.35)</td>
<td>57.65(27.10)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>46.02(14.98)</td>
<td>46.56(23.52)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression/Dejection Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.88(6.11)</td>
<td>16.69(6.98)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>19.00(8.50)</td>
<td>19.62(4.68)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>15.33(3.79)</td>
<td>16.00(7.46)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns= not significant
Table 6.18.(Cont’d). *Patient reported measures means (standard deviations) for the PEG IFN + RBV (Study 1) and triple therapy (Study 2).*

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV (Study 1) Mean (SD)</th>
<th>Triple therapy (Study 2) Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUALITY OF LIFE INVENTORY(QOLI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger/Hostility Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.32(1.03)</td>
<td>8.49(3.11)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>10.57(2.67)</td>
<td>10.22(3.80)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>7.68(0.49)</td>
<td>7.93(2.93)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion/Bewilderment Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.56(3.95)</td>
<td>9.04(3.47)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>9.70(2.48)</td>
<td>9.70(3.68)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>9.52(2.98)</td>
<td>9.48(3.38)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Inertia Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.52(4.12)</td>
<td>11.17(4.85)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>12.93(2.35)</td>
<td>12.94(5.64)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>12.01(2.93)</td>
<td>11.52(5.12)</td>
<td>ns</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension/Anxiety Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.22(4.09)</td>
<td>13.30(4.90)</td>
<td>.05</td>
</tr>
<tr>
<td>End of treatment</td>
<td>14.02(3.48)</td>
<td>13.70(5.25)</td>
<td>.05</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>11.49(3.63)</td>
<td>12.22(4.40)</td>
<td>.05</td>
</tr>
<tr>
<td>PROFILE OF MOOD STATES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigour /Activity Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.64(3.68)</td>
<td>10.84(1.75)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>8.12(1.67)</td>
<td>7.92(1.28)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>9.99(2.36)</td>
<td>10.37(1.82)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*ns= not significant*
Table 6.18. (Cont’d). Patient reported measures means (standard deviations) for the PEG IFN + RBV (Study 1) and triple therapy (Study 2).

<table>
<thead>
<tr>
<th>Measure</th>
<th>PEG IFN + RBV (Study 1) Mean (SD)</th>
<th>Triple therapy (Study 2) Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) DEPRESSION INDEX (range 0-21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.56(2.31)</td>
<td>5.52(2.89)</td>
<td>ns</td>
</tr>
<tr>
<td>End treatment</td>
<td>7.28(1.77)</td>
<td>7.56(3.11)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>5.40(1.35)</td>
<td>5.85(0.95)</td>
<td>ns</td>
</tr>
<tr>
<td>HOSPITAL ANXIETY &amp; DEPRESSION SCALE (HADS) ANXIETY INDEX (range 0-21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.36(2.06)</td>
<td>6.26(1.86)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>8.16(2.10)</td>
<td>8.19(2.08)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>6.40(2.02)</td>
<td>6.22(1.48)</td>
<td>ns</td>
</tr>
<tr>
<td>ADDENBROOKE’S COGNITIVE EXAMINATION-REVISED (ACE-R) (range 0-100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93.92(3.49)</td>
<td>93.04(3.90)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>92.44(3.36)</td>
<td>91.37(4.05)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>94.36(2.58)</td>
<td>94.19(2.42)</td>
<td>ns</td>
</tr>
<tr>
<td>TRAIL MAKING TEST TMT-PART A (range n/a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>34.76(10.65)</td>
<td>34.04(9.34)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>34.76(11.06)</td>
<td>36.37(6.43)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>33.20( 9.55)</td>
<td>32.11 (5.79)</td>
<td>ns</td>
</tr>
<tr>
<td>TRAIL MAKING TEST TMT-PART B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>88.08(34.82)</td>
<td>82.74(24.98)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>92.00(33.87)</td>
<td>94.59(20.57)</td>
<td>ns</td>
</tr>
<tr>
<td>3-month post treatment</td>
<td>83.24(32.44)</td>
<td>79.15(15.04)</td>
<td>ns</td>
</tr>
<tr>
<td>PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 16-80</td>
<td>32.88(6.48)</td>
<td>29.22(11.30)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline</td>
<td>33.28(8.07)</td>
<td>32.85(14.37)</td>
<td>ns</td>
</tr>
<tr>
<td>End of treatment</td>
<td>35.44(6.92)</td>
<td>35.11( 6.59)</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns= not significant
Hypothesis 6

*Compared to PEG IFN + RBV, triple therapy will have a higher percentage of patients who do not complete therapy but will have a higher percentage of patients who achieve SVR for those patients who complete therapy.*

Table 6.19 sets out the numbers and percentage of patients who discontinued therapy and those who achieved SVR. A higher percentage of patients in the triple therapy study group discontinued therapy before treatment ended (22.9%) compared to PEG IFN + RBV (Study 1) (13.3%, $p < .05$). The percentage of patients who achieved SVR based on the number of patients who commenced therapy was 62.8% and 56.7% ($p < .05$) for the triple therapy (Study 2) and the PEG IFN + RBV (Study 1) respectively. When the percentages are calculated on the number of patients completing therapy then those patients in the triple therapy (Study 2) had a higher percentage of patients who achieved SVR (81.5%) than those patients in the PEG IFN + RBV (Study 1) (68.0%, $p < .05$).

Table 6.19. *Comparison of PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients discontinuing therapy and patients achieving SVR*

<table>
<thead>
<tr>
<th></th>
<th>PEG IFN + RBV</th>
<th>Triple Therapy</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients discontinuing therapy before treatment end</td>
<td>4(13.3%)</td>
<td>8(22.9%)</td>
<td>.05</td>
</tr>
<tr>
<td>Number of patients achieving SVR- (% of total starting treatment)</td>
<td>17(56.7%)</td>
<td>22(62.8%)</td>
<td>.05</td>
</tr>
<tr>
<td>% of patients completing treatment who achieved SVR</td>
<td>68.0%</td>
<td>81.5%</td>
<td>.05</td>
</tr>
</tbody>
</table>
GLM between group with repeated measures were computed in order to test hypothesis 5. Within the PEG IFN +RBV (Study 1) and the triple therapy (Study 2) those who achieved SVR (responders) and non-responders were compared over the three time periods; baseline, treatment end and three-month follow-up, in order to determine if those patients achieving SVR, compared to non-responders, reported more improved psychological symptoms at three-month follow-up compared to baseline (see Tables 6.24 and 6.25).

Hypothesis 7:

Compared to non-responders, patients who achieve SVR after being treated with PEG IFN + RBV therapy and triple therapy will report more improved psychological symptoms at three-month follow-up compared to pre-treatment (baseline).

GLM within group with repeated measures were computed in order to test hypothesis 7. The two groups; those who achieved SVR (responders) and non-responders were compared over the three time periods; baseline, treatment end and three-month follow-up, in order to determine if those patients achieving SVR, compared to non-responders, reported more improved psychological symptoms at three-month follow-up compared to baseline (see Tables 6.20 to 6.23).

6.8.1 PEG IFN + RBV (STUDY 1)

Overall for both those patients achieving SVR and non-responders, there were significant changes between baseline and three-month follow-up in the mean scores in the measures FSS and the POMS scales; Anger/Hostility, Confusion/Bewilderment, and Fatigue/Inertia (see Tables 6.20 and 6.21). There was also a significant change between three-
month follow-up and baseline for patients achieving SVR in the POMS Tension/Anxiety scale (see Table 6.20). For non-responders there were also significant changes between baseline and three-month follow-up for the PSQI, POMS scale Vigour/Activity, HADS Depression and Anxiety scales, and the TMT B test (see Table 6.21).

There were insufficient numbers of non-responders to conduct a meaningful GLM between group repeated measures to determine whether changes in reported mean scores between patients achieving SVR and non-responders for any of the psychological symptoms, between 3-month follow-up and baseline was significant.

The change in the mean scores, over the three time points, for each psychological symptom for those patients reporting achieving of SVR and non-responders for PEG IFN + RBV (Study 1) are presented in Tables 6.20 and 6.21 and Appendix Figures N.17 to N.32. Those figures demonstrate there were no interactions for any of the psychological symptoms over the time periods measured. Those patients who achieved SVR reported less psychological symptoms in fatigue, sleep disorders, mood state disturbances (TMD) (including POMS scales Depression/Dejection, Anger/Hostility, Confusion/Bewilderment, Fatigue/Inertia, Tension/Anxiety), depression and anxiety at all 3 time points, but there were insufficient numbers of non-responders to calculate a meaningful independent samples t-test to determine if these differences at any time point were significant. Furthermore, patients who achieved SVR reported higher scores in QOL, Vigour, Activity (POMS Vigour/Activity scale), and TMT A and B tests at all 3 time points but again there were insufficient numbers of non-responders to calculate a meaningful independent samples t-test to determine if these differences at any time point were significant. Interestingly, patients who achieved SVR scored lower on cognitive function, as measured by ACE-R, at all 3 time points compared to
Table 6.20. *Difference in SVR (responders) baseline means versus treatment end (A), treatment end versus three-month follow-up (B) and three-month follow-up versus baseline (C) for PEG IFN + RBV (Study 1) (N = 17).*

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>-1.02*</td>
<td>0.89*</td>
<td>-0.13</td>
</tr>
<tr>
<td>FSS</td>
<td>1.53*</td>
<td>-0.36*</td>
<td>1.17*</td>
</tr>
<tr>
<td>PSQI</td>
<td>2.53*</td>
<td>-2.48*</td>
<td>0.05</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>15.50*</td>
<td>-14.22*</td>
<td>1.28</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>4.18*</td>
<td>-4.05*</td>
<td>0.13</td>
</tr>
<tr>
<td>POMS Anger/Hostility Scale</td>
<td>1.80*</td>
<td>-3.07*</td>
<td>-1.27*</td>
</tr>
<tr>
<td>POMS Confusion/Bewilderment Scale</td>
<td>1.24*</td>
<td>-0.62*</td>
<td>0.62*</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>2.52*</td>
<td>-1.26*</td>
<td>1.26*</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>1.97*</td>
<td>-3.04*</td>
<td>-1.07*</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>-3.59*</td>
<td>1.75*</td>
<td>-1.84*</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>1.70*</td>
<td>-1.70*</td>
<td>0.00</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>1.71*</td>
<td>-1.88*</td>
<td>-0.17</td>
</tr>
<tr>
<td>ACE-R</td>
<td>-1.59*</td>
<td>1.83*</td>
<td>0.50</td>
</tr>
<tr>
<td>TMT A</td>
<td>0.00</td>
<td>-1.56</td>
<td>-1.56</td>
</tr>
<tr>
<td>TMT B</td>
<td>4.11*</td>
<td>-9.47*</td>
<td>-5.36</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>0.83</td>
<td>1.64</td>
<td>2.47</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the .05 level.
Table 6.21. *Difference in non-responders baseline means versus treatment end (A), treatment end versus three-month follow-up (B) and three-month follow-up versus baseline (C) for PEG IFN + RBV therapy (Study 1) (N = 9)*

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>-0.75*</td>
<td>.70*</td>
<td>-0.05</td>
</tr>
<tr>
<td>FSS</td>
<td>1.25*</td>
<td>-0.82</td>
<td>0.43*</td>
</tr>
<tr>
<td>PSQI</td>
<td>4.17*</td>
<td>-2.55*</td>
<td>1.62*</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>12.84*</td>
<td>-9.64*</td>
<td>3.20</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>2.83*</td>
<td>-4.81*</td>
<td>-1.98</td>
</tr>
<tr>
<td>POMS Anger/Hostility Scale</td>
<td>3.20*</td>
<td>-2.50*</td>
<td>0.70*</td>
</tr>
<tr>
<td>POMS Confusion/Bewilderment Scale</td>
<td>0.93*</td>
<td>-1.36*</td>
<td>-0.43*</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>1.56*</td>
<td>-0.21</td>
<td>1.35*</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>1.47*</td>
<td>-1.48*</td>
<td>-0.01</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>-3.37*</td>
<td>2.11*</td>
<td>-1.26*</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>3.60*</td>
<td>-3.20*</td>
<td>-0.50*</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>3.40*</td>
<td>-2.80*</td>
<td>0.49*</td>
</tr>
<tr>
<td>ACE-R</td>
<td>-1.25*</td>
<td>2.10*</td>
<td>0.85</td>
</tr>
<tr>
<td>TMT A</td>
<td>-0.50</td>
<td>-1.12</td>
<td>-1.62</td>
</tr>
<tr>
<td>TMT B</td>
<td>3.50*</td>
<td>-7.25*</td>
<td>-3.75*</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>-0.50</td>
<td>2.25</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the .05 level.
Interestingly, patients who achieved SVR scored lower on cognitive function, as measured by ACE-R, at all three time points compared to non-responders and reported more treatment dissatisfaction at all time points compared to non-responders, however in both cases the differences at all three time points were not significant.

and reported more treatment dissatisfaction at all time points compared to non-responders.

The non-responders changes in impairments from baseline to three-month follow-up were worse for than those achieving SVR for the following measures: PSQI, POMS TMD, POMS scales: Anger/Hostility, Fatigue/Inertia, Tension/Anxiety, HADS Anxiety scale, ACE-R, TMT Part A, and PSQ-18. The changes in impairments from baseline to three-month follow-up were worse for achieving SVR than non-responders for the following measures: the FSS, the POMS scales: Confusion/Bewilderment, Vigour/Activity, the HADS Depression scale and TMT Part B (see Tables 6.20 and 6.21). There were insufficient numbers of non-responders to calculate a meaningful independent samples t-test to determine if these differences in changes between the two studies baseline and three-month follow-up were significant.

6.8.2 TRIPLE THERAPY (STUDY 2)

Overall, for both those patients achieving SVR and non-responders, there were significant changes between baseline and three-month follow-up in the mean scores in the measures FSS and the POMS scales: Anger/Hostility, Confusion/Bewilderment, Fatigue/Inertia, Tension/Anxiety and Vigour/Activity (see Tables 6.22 and 6.23). For non-responders there were significant changes between baseline and three-month follow-up for the QOLI, PSQI, HADS Anxiety scale and the TMT Part B (see Table 6.23).

There were insufficient numbers of non-responders to conduct a meaningful GLM between group repeated measures to determine whether changes in reported mean scores
between patients achieving SVR and non-responders for any of the psychological symptoms, between 3-month follow-up and baseline was significant.

The change in the mean scores, over the three time points, for each psychological symptom for those patients reporting achieving of SVR and non-responders for triple therapy (Study 2) are presented in Tables 6.22 and 6.23 and Appendix Figures N.33 to N.48. Those figures demonstrate there were no interactions for any of the psychological symptoms over the time periods measured. Those patients who achieved SVR reported less psychological symptoms in fatigue, sleep disorders, mood state disturbances (TMD) (including POMS scales Depression/Dejection, Anger/Hostility, Confusion/Bewilderment, Fatigue/Inertia, Tension/Anxiety), depression and anxiety at all 3 time points, but there were insufficient numbers of non-responders to calculate a meaningful independent samples t-test to determine if these differences at any time point were significant. Furthermore, patients who achieved SVR reported higher scores in QOL, Vigour, Activity (POMS Vigour/Activity scale), and TMT Part B at all 3 time points but again there were insufficient numbers of non-responders to calculate a meaningful independent samples t-test to determine if these differences at any time point were significant. Interestingly, patients who achieved SVR scored lower on cognitive function, as measured by ACE-R, and TMT Part A at all 3 time points compared to non-responders and reported more treatment dissatisfaction at all three time points compared to non-responders.

The changes in impairments from baseline to three-month follow-up were worse for non-responders than those achieving SVR for the following measures: QOLI, FSS, PSQI, POMS TMD, POMS scales: Fatigue/Inertia, HADS Anxiety scale, and the ACE-R. The changes in impairments from baseline to three-month follow-up were worse for achieving SVR than non-responders for the following measures: POMS scales: Depression/Dejection, Anger/Hostility, Confusion/Bewilderment, Tension/Anxiety and
Table 6.22. *Difference in SVR(responders) baseline means versus treatment end (A), treatment end versus three-month follow-up (B) and baseline versus three-month follow-up (C) for triple therapy (Study 2) (N = 22)*

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>-1.06*</td>
<td>0.95*</td>
<td>-0.11</td>
</tr>
<tr>
<td>FSS</td>
<td>1.23*</td>
<td>-0.78*</td>
<td>0.45 *</td>
</tr>
<tr>
<td>PSQI</td>
<td>3.04*</td>
<td>-2.54*</td>
<td>0.50</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>10.36*</td>
<td>-10.89*</td>
<td>-0.53</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>2.05*</td>
<td>-2.73*</td>
<td>-0.68</td>
</tr>
<tr>
<td>POMS Anger/Hostility Scale</td>
<td>1.72*</td>
<td>-2.32*</td>
<td>-0.60 *</td>
</tr>
<tr>
<td>POMS Confusion/Bewilderment Scale</td>
<td>0.72*</td>
<td>-0.27*</td>
<td>0.45 *</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>1.68*</td>
<td>-1.39*</td>
<td>0.29 *</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>0.39*</td>
<td>-1.41*</td>
<td>-1.02 *</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>-2.94*</td>
<td>2.45*</td>
<td>-0.49 *</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>2.22*</td>
<td>-1.36*</td>
<td>0.86</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>1.59*</td>
<td>-1.77*</td>
<td>-0.18</td>
</tr>
<tr>
<td>ACE-R</td>
<td>-2.60*</td>
<td>4.00*</td>
<td>1.40</td>
</tr>
<tr>
<td>TMT Part A</td>
<td>2.27</td>
<td>-3.85</td>
<td>-1.58</td>
</tr>
<tr>
<td>TMT Part B</td>
<td>9.96*</td>
<td>-12.14*</td>
<td>-2.18</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>9.00</td>
<td>-2.40</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the .05 level.
Table 6.23. *Difference in non-responders baseline means versus treatment end (A), treatment end versus three-month follow-up (B) and baseline versus three-month follow-up (C) for triple therapy (Study 2) (N = 5)*

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>-0.84*</td>
<td>.02</td>
<td>-0.82*</td>
</tr>
<tr>
<td>FSS</td>
<td>0.80*</td>
<td>.00</td>
<td>0.80*</td>
</tr>
<tr>
<td>PSQI</td>
<td>6.40*</td>
<td>-4.40*</td>
<td>2.00*</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>16.26*</td>
<td>-12.00*</td>
<td>4.26</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>3.46*</td>
<td>-4.20*</td>
<td>-0.74</td>
</tr>
<tr>
<td>POMS Anger/Hostility Scale</td>
<td>1.78*</td>
<td>-2.20*</td>
<td>-0.42*</td>
</tr>
<tr>
<td>POMS Confusion/Bewilderment Scale</td>
<td>0.40*</td>
<td>.00</td>
<td>0.40*</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>2.18*</td>
<td>-1.60*</td>
<td>0.58*</td>
</tr>
<tr>
<td>POMS Tension/Anxiety Scale</td>
<td>.43*</td>
<td>-1.80*</td>
<td>-1.37*</td>
</tr>
<tr>
<td>POMS Vigour/Activity Scale</td>
<td>-2.80*</td>
<td>3.40*</td>
<td>-0.40*</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>3.60*</td>
<td>-3.20*</td>
<td>0.40</td>
</tr>
<tr>
<td>HADS Anxiety Scale</td>
<td>3.40*</td>
<td>-2.80*</td>
<td>0.60*</td>
</tr>
<tr>
<td>ACE-R</td>
<td>-1.46*</td>
<td>2.55*</td>
<td>1.09</td>
</tr>
<tr>
<td>TMT Part A</td>
<td>2.76</td>
<td>-6.16*</td>
<td>-3.40</td>
</tr>
<tr>
<td>TMT Part B</td>
<td>20.20*</td>
<td>-30.00*</td>
<td>-9.80*</td>
</tr>
<tr>
<td>PSQ-18</td>
<td>2.41</td>
<td>3.32</td>
<td>5.73</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the .05 level.*
Vigour/Activity, the HADS Depression scale and TMT Parts A and B and PSQ-18 (see Tables 6.22 and 6.23).

There were insufficient numbers of non-responders to determine whether there were any significant differences in mean scores at baseline or three-month follow-up between those who achieved SVR and non-responders.

6.9 SECTION NINE

SVR PATIENT REPORTED MEASURE’S MEANS AT THREE-MONTH FOLLOW-UP COMPARED TO NORMATIVE MEANS

Hypothesis 8

In both the PEG IFN + RBV (Study 1) and triple therapy (Study 2), at 3-months follow-up to treatment end, for patients achieving SVR there will be an impairment of psychological symptoms compared to normative means

The means for each measure reported by patients who achieved SVR, for both study groups for the three-months follow-up, was collected from data from the GLM repeated measures between subject’s analysis and are presented in Table 6.30. Also presented in Table 6.30 are the normative means or range of means, of each measure to demonstrate the impairment of psychological symptoms, at 3-months follow-up, for those patients who had achieved SVR. This comparison highlights ongoing impairment with both therapies in most psychological symptoms measured in this study, but highlights significant impairment with fatigue and sleep problems.

The QOLI mean scores for PEG IFN + RBV (Study 1) and triple therapy (Study 2) are 2.00 and 2.11 respectively. This is at the low end of the range of 2 – 3.75 which represents the typical score for adults. The FSS mean scores for PEG IFN + RBV (Study 1) and triple therapy (Study 2) are
Table 6.24. *PEG IFN + RBV (Study 1) and triple therapy (Study 2)* means at three-month follow-up for patients achieving SVR, compared to normative means.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean for PEG IFN + RBV achieving SVR (N=17)</th>
<th>Mean for triple therapy achieving SVR (N=22)</th>
<th>Normative mean (Standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLI</td>
<td>2.00</td>
<td>2.11</td>
<td>2-3.75 range</td>
</tr>
<tr>
<td>FSS</td>
<td>4.95</td>
<td>4.95</td>
<td>2.30 (0.70)</td>
</tr>
<tr>
<td>PSQI</td>
<td>7.76</td>
<td>8.05</td>
<td>2.67 (1.70)</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>41.22</td>
<td>43.14</td>
<td>12.70 (29.60)</td>
</tr>
<tr>
<td>POMS Depression/Dejection Scale</td>
<td>14.48</td>
<td>15.54</td>
<td>7.10 (8.40)</td>
</tr>
<tr>
<td>POMS Anger/Hostility Scale</td>
<td>6.85</td>
<td>7.50</td>
<td>6.60 (6.70)</td>
</tr>
<tr>
<td>POMS Confusion/Bewilderment Scale</td>
<td>8.56</td>
<td>9.09</td>
<td>5.20 (4.10)</td>
</tr>
<tr>
<td>POMS Fatigue/Inertia Scale</td>
<td>11.38</td>
<td>10.77</td>
<td>7.30 (5.70)</td>
</tr>
<tr>
<td>POMS Tension/Anxiety</td>
<td>10.26</td>
<td>11.68</td>
<td>7.00 (5.50)</td>
</tr>
<tr>
<td>POMS Vigour/Activity</td>
<td>10.22</td>
<td>10.45</td>
<td>20.20 (6.20)</td>
</tr>
<tr>
<td>HADS Depression Scale</td>
<td>5.06</td>
<td>5.59</td>
<td>0-7 range</td>
</tr>
<tr>
<td>HADS: Anxiety Scale</td>
<td>5.71</td>
<td>5.82</td>
<td>0-7 range</td>
</tr>
<tr>
<td>ACE-R</td>
<td>94.12</td>
<td>93.00</td>
<td>96.00 (2.70)</td>
</tr>
<tr>
<td>TMT Part A</td>
<td>33.20</td>
<td>32.55</td>
<td>29.0</td>
</tr>
<tr>
<td>TMT Part B</td>
<td>86.88</td>
<td>78.27</td>
<td>75.0</td>
</tr>
<tr>
<td>PSQI-18</td>
<td>36.35</td>
<td>36.00</td>
<td>50.20 (11.67)</td>
</tr>
</tbody>
</table>

Both 4.95. This compares to a FSS mean score for healthy adults of 2.30 (*SD = 0.70*) and 4.50 for depression alone (without fatigue associated conditions) and 5.40 for clinically significant fatigue.

Furthermore, the overall mean scores for the PSQI measuring sleep disorders for PEG IFN + RBV (Study 1) and triple therapy (Study 2) were 7.76 and 8.05 respectively. The normative mean score for the PSQI measure is 2.67 (*SD = 1.70*). A mean score of 6.53 is the cut off for EDS. Patients for both treatments have reported mean scores above that for EDS.

All the POMS scales for both studies show mean scores below that of the normative mean.

Both the depression and anxiety scales of the HADS measure recorded mean scores within the range interpreted as normal although the mean scores for both therapies is at the upper level of the range. A
mean score of between 8 and 10 in the depression scale is an indication of possible clinical depression.

A lower score on the ACE-R measure indicates less cognitive skills. The mean scores reported for both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) were lower than the normative mean. Also, lower scores on both the TMT Part A and TMT Part B indicate more cognitive skills. In both studies the mean scores for the TMT Part A and TMT Part B were above the normative mean.

Finally, the PSQ-18 which measures patient satisfaction with a higher score indicating more dissatisfaction with treatment. In both studies the reported mean scores were below the normative mean indicating better treatment satisfaction that the normative mean.
CHAPTER SEVEN
DISCUSSION

7.0 INTRODUCTION

The present study sought to determine the relationship between the psychological symptoms of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, cognitive functioning and patient satisfaction and PEG IFN + RBV and triple therapies. Using baseline, end of treatment and three-month follow-up data collected from HCV patient’s reported measures this study had a number of objectives: first, the examination of the sociodemographic and clinical characteristics, QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, cognitive functioning and patient satisfaction in patients with HCV infection who were presenting for PEG IFN + RBV and triple therapy treatments; second, to investigate changes in these psychological symptoms between baseline and end of treatment and three-month follow-up in patients being treated with these therapies; third, to investigate the differences in the psychological symptoms of PEG IFN + RBV and triple therapies for those patients who achieved SVR and those who did not (non-responders).

Further objectives of this study included a comparison of the psychological symptoms of both therapies at baseline, treatment end and at three-month follow-up, and whether there was a difference in the percentage of patients who achieved SVR in PEG IFN + RBV compared to triple therapy.

The findings of the present study will be discussed in the context of previous studies and empirical research. Following these discussions, the contributions of the current research to the literature will be considered, together with the limitations of the study. Finally, general conclusions and recommendations for future research will be presented.
7.1 STUDY FINDINGS

7.1.1 COMPARISON OF PSYCHOLOGICAL SYMPTOMS OF HCV PATIENTS PRESENTING FOR TREATMENT TO PSYCHOLOGICAL SYMPTOMS OF NORMATIVE POPULATION

The present study hypothesised that the psychological symptoms reported by patients presenting for PEG IFN + RBV therapy and triple therapy would be poorer than other norm referenced clinical populations of the standardised measures of QOL, fatigue, sleep disorders, mood state disturbance, depression, anxiety, and cognitive function.

The study’s findings support this hypothesis for all the aforementioned standardised measures. At baseline the overall QOLI mean scores for the PEG IFN + RBV (Study 1) and triple therapy (Study 2) were 1.86 and 1.97 respectively. QOLI mean scores of between 2 and 3.75 are considered to be representative of typical mean scores for adults. Higher mean scores in the QOLI represent a better QOL. The overall QOLI mean scores reported by PEG IFN + RBV (Study 1) and triple therapy (Study 2) patients were below the typical score for the adult population. These findings are consistent with previous research which has found the presence of HCV even at the early stage of the disease is associated with worse HRQL (Foster et al., 1998; Kenny-Walsh, 1999; McHutchison et al., 2001; Strauss et al., 2014; von Wagner et al., 2006; Wiese et al., 2000) and that HCV infection without comorbidity was associated with impaired QOL (Rodger et al., 1999).

In this research the subjective symptom of fatigue was assessed using the objective FSS questionnaire and the POMS Fatigue/Inertia scale. HCV-infected patients presenting for treatment for both therapies reported more fatigue than the normative mean score for healthy individuals. Previous studies have also shown that fatigue is one of the most disabling and frequently reported symptoms of HCV (Barkhuizen et al., 1999; Forton et al., 2003; Glacken
et al., 2003; Hassoum et al., 2002; Hilsabeck et al., 2007; Kallman et al., 2007; Kramer et al., 2005; Poynard et al., 2002; Teuber et al., 2008)

The effect of sleep disorders in patients with HCV infection is not well understood. In this study, more sleep disorders were reported by patients presenting for both therapies than was the normative mean. Of those patients presenting for treatment, 56.6% of the PEG IFN + RBV therapy (Study 1) and 60.0% of the triple therapy (Study 2) scored higher than the 6.53 cut-off for disorders of excessive daytime somnolence on the PSQI measure. This mean score compares to a PSQI of 2.67 for normal sleep function. Previous studies have also demonstrated sleep disorders in a high percentage of persons with HCV infection. (M. Carlson et al., 2004; Clifford et al., 2005; De Cruz et al., 2012; Heeren et al., 2014; C. Lang et al., 2006; Weissenborn et al., 2009; Yoh et al., 2016).

Findings from this research showed all 6 scales in the POMS questionnaire used in the PEG IFN + RBV therapy study were impaired compared to normative healthy adults and were further impaired in all scales, except the Tension/Anxiety scale, when compared to a normative pain patient group. A review of literature found one study which found mood disorders were frequent in patients with CHC (Constant et al., 2005).

It was also found that patient reports of depression were close to the norm, however an analysis of the data revealed that close to 50% of the PEG IFN + RBV (Study 1) patients and approximately 45% of the triple therapy (Study 2) patients neared the cut off score of 8 indicating possible clinical depression. Using the POMS Depression / Dejection scale the patients in both therapies reported a mean score above that of the normative mean for pain patients. These findings are consistent with other studies which have measured depression in patients with HCV infection and found depression is higher in that population than in the normative population (Batista-Neves et al., 2008; Carta et al., 2007; Erim et al., 2010; Zignego et al., 2007).
While anxiety is a separate diagnosis to depression, similar trends to depression were found. Overall on average, patients for both studies reported normal scores on the HADS anxiety scales. An analysis of the data showed close to 47% of the PEG IFN + RBV (Study 1) patients and approximately 54% of the triple therapy (Study 2) patients neared the cut off score of 8 which indicates possible clinical anxiety. Using the POMS Tension/Anxiety scale the patients in both therapies reported a mean score above that of healthy older adults. These findings are consistent with previous studies which found anxiety was higher in persons with HCV infection than in both the normative population (Batista-Neves et al., 2008) and in healthy control groups.

Patients in both the PEG IFN +RBV (Study 1) and triple therapy (Study 2), at baseline, scored significantly below the overall normative score mean in the ACE-R measure. An analysis of the factors in that measure showed that memory and verbal fluency were the two factors in the two studies which were significantly lower than normative means. At baseline there was no significant difference in the mean scores for the three factors; Attention/Orientation, Language and Visuospatial when compared to normative mean scores. For both studies and for both the TMT Parts A and B (measuring attention, speed and mental flexibility), patient’s overall mean showed more impaired cognitive function compared to normative means, but the differences were not significant. These findings are consistent with previous studies which have measured cognitive functioning in patients with HCV infection and found that cognitive function is impaired in verbal learning, verbal fluency, memory and attention (Fontana et al., 2005; Forton et al., 2003; Kramer et al., 2002; Kramer et al., 2005; B. M. Spiegel et al., 2005; Tillman et al., 2011; Weissenborn et al., 2004; Weissenborn et al., 2009). Furthermore, the findings of this study’s research are consistent with the Foster (2009) study which found HCV patients were impaired in their mental health compared to their
physical health, which is in contrast to other chronic illnesses where mental impairment is less evident than physical impairment.

Two studies contrasted with the present study’s findings and the findings of most of the previous studies which have investigated cognitive function in HCV patients. Cordoba and colleagues (2003) reported HCV-infected patients’ neurocognitive results were no different from those of healthy controls and McAndrews and colleagues (2005) reported cognitive dysfunction in HCV-infected patients showed little clinical significance. The Cordoba and colleagues (2003) study included a low percentage of ex-injecting drug user participants, but other than that, there was no explanation offered why their results differed from most prior studies and the present study.

7.1.2 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The present study hypothesised there would be no association between sociodemographic factors at baseline and the severity of symptoms reported by patients presenting for PEG IFN + RBV (Study 1) and triple therapy (Study 2). The present study findings supported this hypothesis. For HCV-infected patients who presented for PEG IFN + RBV therapy and triple therapy, there were no sociodemographic factors which showed any relationship to the psychological symptoms: QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function, or patient treatment satisfaction. The sociodemographic factors analysed were gender, age, marital status, educational history, a history of injecting drug use, being prescribed antidepressants for current treatment, a history of antidepressant drug usage, and the use of non-prescription drugs at the time of presenting for therapy.

The most common form of transmission of HCV is through injecting drug use (Law et al., 2003), therefore it is not unexpected that 25 (83.3%) of the PEG IFN + RBV (Study 1) and 28 (80.0%) of the triple therapy (Study 2) patients contracted the virus through injecting drug
use. This study included 19 (63.3%) males in the PEG IFN + RBV (Study 1) and 27(77.1%) males in the triple therapy (Study 2). Statistically the prevalence of HCV infection is higher in males (Butterfield et al., 2003). While triple therapy is limited to HCV genotype 1 patients, PEG IFN + RBV is available to patients with other genotypes. In the PEG IFN + RBV (Study 1), 24 (80.0 % ) of patients were genotype 1. Genotype 1 is the most prevalent genotype in New Zealand (Gane, 2008).

No relationship between gender and any of the psychological symptoms being measured was revealed by correlation analysis. The reporting of no significant gender difference in the present study may be partially explained by the findings of Hannay (1978). That study reported that gender difference in symptom reporting disappeared after the age of 45. The disappearance of gender difference after the age of 45 may also be due to the reduction of estrogen in females ≥ 50 years (Sezaki et al., 2009). Hayashi and colleagues (1998) reported treatment with IFN was more successful for females younger than 39 years of age compared to females over the age of 39. The mean age of the present study’s population was in the mid-forties.

7.1.3 CORRELATIONS BETWEEN QOL AND PSYCHOLOGICAL SYMPTOMS INCLUDING FATIGUE AND SLEEP DISORDERS, MOOD STATE DISTURBANCE, DEPRESSION AND ANXIETY, COGNITIVE FUNCTION, AND PATIENT SATISFACTION AT BASELINE FOR PEG IFN + RBV THERAPY AND TRIPLE THERAPY PATIENTS

This study hypothesised there would be a significant correlation between QOL, as a measure of satisfaction, and psychological symptoms including fatigue, sleep disorders, mood state disturbance, depression, anxiety, cognitive function and patient satisfaction at baseline for PEG IFN + RBV therapy and triple therapy patients.

The present study’s findings in most cases supported this hypothesis. Pearson’s correlations coefficients were computed to investigate the hypothesis and it was found for
both PEG IFN + RBV (Study 1) and triple therapy (Study 2), at baseline, that QOL had a negative correlation with fatigue, sleep disorders, POMS TMD and all of the POMS scales except Vigour/Activity, depression and anxiety. Furthermore, the present study showed a positive correlation with cognitive function. There was also a negative correlation with the TMT Part B (improved QOL was associated with less time to complete the TMT B). For both studies, there was no association between the POMS scale Vigour/Activity, TMT A and patient dissatisfaction. All of the correlations were, in most cases, consistent over the three time periods. It is interesting to note that TMT Part B was associated with QOL but TMT Part A was not. The TMT Part A test is relatively easy test, which suggests that there was an impairment to cognitive function requiring more concentration, but not to cognitive function related to performing simpler tasks.

These finding are consistent with previous research that has reported HRQL is associated with fatigue (Gutteling et al., 2006; Kallman et al., 2007; Younossi et al., 2014a) sleep disorders (Younossi et al., 2014a) and depression (Younossi et al., 2014a). These findings are also consistent with previous research which has found the presence of HCV even at the early stage of the disease is associated with worse QOL (Foster et al., 1998; Kenny-Walsh, 1999; McHutchison et al., 2001; Strauss et al., 2014; von Wagner et al., 2006; Wiese et al., 2000) and also that HCV infection without comorbidity was associated with impaired QOL (Rodger et al., 1999).

7.1.4 PSYCHOLOGICAL SYMPTOMS AT END OF TREATMENT AND AT THREE-MONTH FOLLOW-UP

The present study hypothesised that patients treated with PEG IFN + RBV therapy and triple therapy would report significantly more impairment of psychological symptoms at treatment end compared to pre-treatment (baseline), but would report a return to pre-
treatment (baseline) levels of psychological symptoms at three-month follow-up to treatment end.

Overall, the hypothesis that patients treated with PEG IFN + RBV therapy and triple therapy would report significantly more impairment of psychological symptoms at treatment end compared to pre-treatment (baseline) was confirmed by the present study’s findings. However, the hypothesis that patients treated with PEG IFN + RBV and triple therapy would report a return to pre-treatment (baseline) levels of psychological symptoms at three-month follow-up to treatment end was only confirmed for the psychological symptoms of depression, anxiety and cognitive function and was not supported for the psychological symptoms of QOL, fatigue, sleep disorders and mood disturbance. The present study showed a non-significant result for the hypothesis for patient satisfaction.

QOL at end of treatment and at three-month follow-up

It was found that QOL decreased significantly from baseline to treatment end for both PEG IFN + RBV (Study 1) and triple therapy (Study 2). Furthermore, there was a significant improvement in QOL from treatment end to three-month follow-up for both studies. However, for both studies, the QOL reported by patients at three-month follow-up was significantly less than reported at baseline. Therefore, the psychological symptom QOL supported the hypothesis at treatment end compared to baseline but not at three-month follow-up compared to baseline.

For both studies, patients achieving SVR reported a lower QOL at three-month follow up than at baseline but the differences between the two time points were not significant. Also, for both studies, patients who achieved SVR at three-month follow-up reported a higher QOL than non-responders. However, at three-month follow-up those patients achieving SVR and non-responders reported QOL mean scores at the lower end of the normative range for adults.
The present study’s results are consistent with previous research investigating PEG IFN + RBV therapy which found significant decrements in HRQL between baseline and treatment end but improved HRQL following end of treatment (Dan et al., 2006; Younossi et al., 2014a). The results are also consistent with a prior boceprevir-based triple therapy study which showed improved HRQL post treatment after a severe decrement in HRQL in the 24 weeks from baseline to treatment (Mousa, 2012).

However, the present study found, for both studies, that at three-month follow-up to treatment end patients were reporting QOL levels significantly below those reported at baseline, although for patients achieving SVR the difference was not significant. These results are consistent with two 2008 studies which reported impairment to HRQL despite HCV patients achieving SVR following IFN + RBV therapy (Heibling et al., 2008; Pattullo et al., 2008) and the Tillman and colleagues (2011) which reported some patients still had impaired HRQL after achieving SVR following IFN + RBV therapy. These three studies used the SF-36 measure.

However, the present study’s results are not consistent with a number of previous studies of HCV therapies. Prior studies have shown patients treated with IFN+ RBV showed significant improvement in HRQL after achieving SVR (McHutchison et al., 2001; Ware et al., 1999). A qualitative study by Hopwood (2009) reported patients who achieved SVR following treatment with PEG IFN + RBV showed improved QOL. Furthermore, a study of patients achieving SVR after SOF+PEG IFN + RBV reported patients HRQL returned to baseline levels (Younossi et al., 2014a). A search of literature revealed no studies which have compared post treatment outcomes to baseline for boceprevir-based triple therapy.

It was not determined why there were differing outcomes in previous quantitative studies, all of which used the SF-36 to measure HRQL. The present study used the QOLI to measure QOL. The SF-36 measures HRQL which includes the Mental Component Summary
comprising: Vitality, Social Functioning, Role Emotional and Mental Health, but also has a strong weighting for the four scales comprising the Physical Component Summary measuring functional abilities and impairments; Physical Functioning, Role Physical, Bodily Pain and General Health. In contrast, the QOLI measures QOL in terms of 16 domains in relation to the satisfaction and the importance a patient places on those domains. The results of the present study showed a high correlation between the overall mean QOL score and patient satisfaction mean score.

Interestingly in the present study for both PEG IFN + RBV (Study 1) and triple therapy (Study 2) the domain Health reported outcomes consistent with previous studies which used the SF-36. The Health domain in the QOLI results showed significant impairment between treatment end and baseline, a significant improvement from treatment end to three-month follow-up and at three-month follow-up an improvement to baseline which was not significant. This domain measures similar aspects for QOL that are reflected in the SF-36.

The present study found for both therapies there was no significant effect between any of the three time points for the seven domains in the QOLI; Money, Work, Children, Relatives, Home, Neighbourhood and Community. Also, other than the domain Relative (reported as important in the PEG IFN + RBV (Study 1)), these domains were not reported by patients as being important to their happiness. This suggests that patient’s overall QOL during the two treatments was not dependent on these domains. It also suggests that, overall, over the course of treatment there was no interest by patients to improve satisfaction in their neighbourhood or community. Furthermore, it also suggests that changes in QOL over the three time periods were dependent on the other QOLI domains: Health, Self-esteem, Goals, Play, Learning, Creativity, Helping, Love, and Friends.

Four domains showed a significant satisfaction impairment at three-month follow-up compared to baseline: Goals, Play, Creativity, and Love and thus would have influenced the
overall QOL reported between baseline and three-month follow-up. Furthermore, for both studies, four domains showed relatively higher importance ratings; Friends, Goals, Self-esteem, and Health. In addition, the domain Relatives and Play were reported as relatively important in the PEG IFN +RBV (Study 1) and triple therapy (Study 2) respectively.

Therefore, except for the domain Health, the domains which were affecting changes in QOL over the 3 time periods in the present study were domains related to the patients’ psychological or psychosocial wellbeing. In contrast the studies using the SF-36 measured changes in HRQL more weighted to a patient’s functional abilities and impairment. Therefore, a reason for any differences in the present study to results in other HCV therapy studies using the SF-36 may be because the studies are measuring different constructs.

Interestingly the domain Goals had a relatively impaired satisfaction rating and a relatively high importance rating and thus has a strong weighting on the over the decrement of the QOL mean score in the present study. The domain Goals in the QOLI measure is defined as beliefs about what matters most in life and how one should live both now and in the future. It includes what a person thinks is right and wrong and the purpose and meaning of life.

Fatigue and sleep disorders at end of treatment and at three-month follow-up

The present study examined the influence of PEG+ IFN + RBV and boceprevir-based triple therapies on fatigue and sleep disorders. Using the FSS to measure fatigue and the PSQI to measure sleep disorders, patients reported significant increases in fatigue and sleep disorders from baseline to treatment end for both therapies. It was also reported that patient’s fatigue and sleep disorders decreased significantly from treatment end to three-month follow-up for both therapies. Furthermore, the POMS Fatigue/Inertia scale showed the same significant changes between the three time periods and the POMS Vigour/Activity scale showed inversely the same significant changes between the three time periods.
At three-month follow-up to treatment end, for both studies, fatigue impairment (measured by FSS, POMS Fatigue/Inertia scale, POMS Vigour/Activity scale) was higher compared to baseline. Sleep disorders at three-month follow-up were significantly worse than baseline for triple therapy (Study 2) and while for the PEG IFN + RBV (Study 1) sleep disorders at three-month follow-up were worse than at baseline the difference was not significant. Other than the non-significant result for the difference in three-month follow-up and baseline for sleep disorders in PEG IFN + RBV (Study 1) the hypothesis is confirmed. While prior evidence has linked fatigue with PEG IFN + RBV therapy during treatment (Heathcote et al., 2000; Maddock et al., 2005; Poynard et al., 2002), to the best knowledge of the author there have been no quantitative studies which have used a fatigue specific measure to examine the relationship between fatigue and PEG IFN + RBV therapy post treatment and SVR. Several studies have used the more generic Vitality scale in the SF-36 measure to investigate fatigue. The Younossi and colleagues (2014a) study found in the PEG IFN + RBV arm of that study no significant difference in the Vitality scale observed at week-12 follow-up compared to baseline. This result is in contrast to the findings of the present study. However, the present study did find fatigue at three-month follow-up was still significantly impaired compared to baseline, a result supported by the Ware and colleagues (1999) study, which reported (using the SF-36 measure), fatigue in patients 24 month after treatment with PEG IFN + RBV.

The present study also investigated with PEG IFN + RBV therapy and triple therapy the effect on fatigue of achieving SVR and whether there was a difference in fatigue for those patients who achieved SVR compared to non-responders. The present study found that at three-month follow-up the fatigue mean score reported by non-responders was greater than reported by those who achieved SVR. Also fatigue mean scores at three-month follow-up were significantly higher than at baseline for both patients achieving SVR and non-
responders. The present study did not have a large enough sample to systematically evaluate whether there was a significant impact on fatigue for those patients achieving SVR compared to non-responders.

The present study used the FSS measure instead of the SF-36 which may account for the differing results of the present study to the findings in the Younossi and colleagues (2014a) study. However, the Ware and colleagues (1999) study which used the Vitality scale of the SF-36 to measure fatigue, found patients who achieved SVR had less fatigue at 24 weeks than non-responders. In that study baseline fatigue levels were similar for both patients achieving SVR and non-responders.

The results of research into ongoing fatigue after PEG IFN + RBV therapy have been reported in two qualitative studies (Hopwood, 2009; The Hepatitis C Trust, 2007), and support the findings of the present study. Both the Hepatitis C Trust (2007) and Hopwood (2009) found that fatigue was the most frequently reported post treatment symptoms of PEG IFN + RBV therapy. At six-month follow-up to treatment end the Hepatitis C Trust (2007) found 72% of participants reporting fatigue. The 72% of patients included those achieving SVR and non-responders. A split between those two groups was not available in the results of that research study.

The findings in this study are consistent with the limited number of previous studies in triple therapies, other than boceprevir-based triple therapy, which have reported fatigue during therapy. One such study found fatigue was a significant side effect during telaprevir-based triple therapy (Fagundes et al., 2015). The current study’s findings at treatment end are also consistent with the Younossi and colleagues (2014a) SOF + RBV +IFN study which found that a significant decrement in the Vitality scale of the SF-36 at treatment end compared to baseline.
The present study also investigated for boceprevir-based triple therapy the impact on fatigue of achieving SVR and whether there was a difference in fatigue for those patients who achieved SVR compared to non-responders. For both patients achieving SVR and non-responders fatigue reported at treatment end was significantly more than at baseline. Also fatigue mean scores at three-month follow-up were significantly lower than at treatment end and significantly higher than at baseline for both patients achieving SVR and non-responders. The current study also found that at treatment end and at three-month follow-up the FSS mean score reported by non-responders was greater than reported by those who achieved SVR. The current study did not have a large enough sample to systematically evaluate whether there was a significant impact on fatigue for those patients achieving SVR compared to non-responders.

At the time of writing, to the best knowledge of the researcher, there were no studies which had investigated fatigue for patients achieving SVR and non-responders at three-month follow-up for boceprevir-based triple therapy. The Younossi and colleagues (2014a) study, while not investigating boceprevir-based triple therapy did investigate SOF-based triple therapy. That study reported significant improvement in the Vitality scale of the SF-36 at 12-week follow-up to the end of treatment compared to pre-treatment in patients who achieved SVR and no meaningful improvement in fatigue was observed at 12-week follow-up compared to baseline.

Despite the importance of sleep in both psychological and physiological health, the review of the literature found no quantitative research relating to ongoing sleep disorders post PEG IFN + RBV therapy. Other quantitative studies have reported insomnia in patients being treated with PEG IFN (Heathcote et al., 2000; Reddy et al., 2001). Furthermore, the review of the literature found no qualitative data relating to sleep disorders and SVR and non-responders in PEG IFN + RBV therapy. However, the results of research into ongoing sleep
disorders after treatment end have been reported in two qualitative studies (Hopwood, 2009; The Hepatitis C Trust, 2007).

A review of the literature found two triple therapy studies which reported on sleep disorders during triple therapy. A previous study found 34% of patients reported insomnia during boceprevir-based triple therapy (Poordad et al., 2011). A second study of patients undergoing simeprevir-based triple therapy found sleep disorders significantly increased at four weeks after the commencement of treatment compared to the patient’s evaluation at baseline (Yoh et al., 2016). Similar to the present study the Yoh and colleagues (2016) study used the PSQI measure. The review of the literature found there are no quantitative boceprevir-based triple therapy studies of sleep disorders at treatment end nor at three-month follow-up.

The results of the Yoh and colleagues (2016) study together with the present study, suggest the onset of significant sleep disorder occurs early in triple therapy and continues through to the end of treatment and then shows a significant improvement between treatment end and three-months follow-up. However, despite the improvement in sleep disorders from treatment end to three-month follow-up, sleep still remains significantly impaired at three-month follow-up compared to baseline following treatment with triple therapies.

Mood state disturbances at end of treatment and at three-month follow-up

The present study found that patients receiving both PEG IFN + RBV therapy and triple therapy reported significant increases in overall total mood disturbances from baseline to treatment end, which were reversed from treatment end to three-month follow-up. This result supports the hypothesis.

The present study’s findings are supported by the findings of Constant and colleagues (2005) who reported mood disorders are common in PEG IFN + RBV therapy and consist of an overlap between depression and manic symptoms rather than a mere depression. They also
reported that irritability, anger, hostility, and manic/hypomanic episodes were common in patients during HCV therapy and neurovegetative symptoms in most patients within four weeks of treatment commencement.

At three-month follow-up to treatment end the mean scores for total mood disturbance were higher than at baseline for both studies but the differences were not significant. This was the case for both those patients achieving SVR and non-responders. This result does not support the hypothesis.

A review of the literature found no quantitative studies investigating mood disorders in PEG IFN + RBV post treatment. The Hepatitis C Trust (2007) qualitative study reported mood swings in 48% of patients with the first 6 months of treatment end follow-up and 23% of patients still experiencing moods swings 12 months or longer after treatment end. A review of the literature found no triple therapy studies which had investigated mood states disturbances.

The results of the six scales comprising the Total Mood State were mixed. All six scales showed a significant impairment from baseline to treatment end. From treatment end to three-month follow-up there was a significant improvement in all mean scores for the six scales except for Confusion/Bewilderment scale. Three of the six scales (Anger/Hostility, Depression/Dejection, Tension/Anxiety) showed three-month follow-up means below baseline, whereas the other three scales (Confusion/Bewilderment, Fatigue/Inertia, Vigour/Activity) showed three-month follow-up means above baseline. The trends for the results for the scales Depression/Dejection and Tension/Anxiety are consistent with the HADS results for the present study and the results for the scales Fatigue/Inertia and Vigour/Activity are consistent with the FSS and PSQI results for the present study.

For both studies the Anger/Hostility scale supported the hypothesis. At treatment end the level of anger and hostility reported was significantly greater than at baseline, but there
was a significant reduction in anger and hostility from treatment end to three-month follow-up. At three-month follow-up anger and hostility had reduced significantly compared to baseline. Possibly the adverse side effects of the therapies may have caused patients anger and hostility at treatment end, especially if the side effects were worse than they had been advised by their healthcare professional. This suggestion is supported by the Anger/Hostility scale mean at baseline and treatment end being above the mean for the pain patient control mean. Anger and hostility reported at three-month follow-up was significantly below baseline and below the mean for the pain patient control. However, the mean score for the Anger/Hostility scale at three-month follow-up neared the mean for the pain patient control.

The Confusion/Bewilderment scale, for both studies, showed significant impairment from baseline to treatment end, supporting the hypothesis. However, whilst there was less impairment in the Confusion/Bewilderment scale from treatment end to three-month follow-up the change was not significant. Also, the three-month follow-up mean was above the baseline mean but the difference was not significant. The mean score at all three time points was above the mean for the pain patient control mean. When comparing the present study’s result to the pain patient control this result is understandable at treatment end, but it is interesting that confusion and bewilderment levels continue through to three-month follow-up at levels above the pain patient control. One suggestion for this result is that patients are still experiencing adverse side effects from HCV treatment.

*Depression and anxiety at end of treatment and at three-month follow-up*

Patients reported that symptoms of depression and anxiety increased significantly from baseline to treatment end for both studies for all the HADS and POMS measures reporting on these two symptoms. These results support the hypothesis and are consistent with prior research studies on depression and to a lesser extent anxiety (Davis et al., 1998; Dieperink et al., 2003; Manns et al., 2001; McHutchison et al., 1998; Raison et al., 2005a).
Furthermore, overall and for those patients achieving SVR, mean scores for three-month follow-up were above baseline means scores for the PEG IFN + RBV (Study 1) for HADS Anxiety scale, and the triple therapy (Study 2) HADS Depression scale. In addition, the present study showed baseline means scores above three-month follow-up mean scores for PEG IFN+ RBV (Study 1) for: HADS Depression scale, POMS Depression/Dejection scale, and POMS Tension/ Anxiety scale, and for triple therapy (Study 2): HADS Anxiety scale, POMS Tension/Anxiety scale, POMS Depression/Dejection scale. In all of the cases the differences were not significant. The only significant difference in any of the depression and anxiety measures was the POMS Tension/Anxiety scale which reported tension and anxiety as significantly less at three-month follow-up than at baseline. For non-responders the depression mean score measured by POMS at three-month follow-up was higher than the baseline mean score, but the difference was not significant. The three-month follow-up and baseline mean scores for non-responders were the same when measured by the HADS depression scale.

Although the overall mean scores at three-month follow-up for the HADS Depression scale, for both those who achieved SVR and non-responders, were below the cut-off mean score of 8 for clinical depression, overall close to 50% of patients reported scores which neared the cut-off score of 8. For the POMS Depression/Dejection scale non-responders scored above the pain population control mean score and those patients who achieved SVR neared the pain population mean score.

The results of research into ongoing depression after PEG IFN + RBV therapy are supported by the findings of two qualitative studies which found that depression was one of the most frequently reported post treatment symptom of PEG IFN + RBV therapy (Hopwood, 2009; The Hepatitis C Trust, 2007). It was also reported in one of the qualitative studies that six months after treatment end more than 50% of participants were reporting
depression (Hopwood, 2009). Kow and colleagues (2010) reported that depression was one of the common psychological adverse events reported by patients as the reason for withdrawal from triple therapy. A review of the literature found no studies which had specifically investigated the relationship between depression, triple therapy, and post treatment outcome.

Research on patient reported anxiety after treatment end is limited. A review of literature found no data on the patient reports of anxiety for PEG IFN + RBV therapy at the three-month post treatment period. The results of research into ongoing anxiety after PEG IFN + RBV therapy have been reported in two qualitative studies (Hopwood, 2009; The Hepatitis C Trust, 2007) and support the findings of the present study. Both the Hepatitis C Trust (2007) and Hopwood (2009) research found that anxiety was a reported post treatment symptom of PEG IFN + RBV therapy. At six-month follow-up to treatment end the Hepatitis C Trust (2007) found patients continued to report symptoms of anxiety.

A review of the literature found no research studies which have investigated anxiety and triple therapy.

*Cognitive function at end of treatment and at three-month follow-up*

An analysis of the ACE-R measure’s mean scores for both the PEG IFN + RBV (Study 1) and triple therapy (Study 2) revealed a significant decrement in overall cognitive function between baseline and treatment end, a significant improvement and cognitive function from treatment end to three-month follow-up. This result supports the hypothesis. Furthermore, while cognitive function at three-month follow-up showed an improvement compared to baseline the difference was not significant, a result which is not consistent with the hypothesis.

For both studies the Trail Making Test Part A showed no difference between any of the three time points. The results varied for each of the two study groups for the more complicated Trail Making Test Part B. For PEG IFN + RBV (Study 1) patients took longer to
complete Trail Making Test Part B at treatment end compared to baseline, indicating impaired attention, speed, and mental flexibility, but the difference was not significant. There was a significant decrease in the time taken to complete Trail Making Test B between treatment end and three-month follow-up. Also, the time taken to complete Trail Making Test B was significantly less at three-month follow-up than at baseline. For the triple therapy (Study 2) the time to complete Trail Making Test Part B was significantly longer at treatment end than at baseline, but improved significantly between treatment end and 3-month follow-up. While the time taken to complete Trail Making Test Part B at three-month follow-up was less than at baseline the difference was not significant.

The current study indicates that cognitive function improves after treatment. However, the current study found the average mean score in cognitive function in memory, verbal fluency, attention, speed, and mental flexibility remained lower at three-month follow-up than the normative mean. The present study also reported no difference at three-month follow-up in cognitive mean scores between those achieving SVR and non-responders. The results of the study indicated that HCV therapy affected cognitive function requiring concentration, attention and orientation skills (tested by the Trail Making Test Part B) compared to cognition that does not rely heavily on these skills (tested by the Trail Making Test Part A). The present study also reported no difference at three-month follow-up in cognitive mean scores between those achieving SVR and non-responders.

Consistent with the ACE-R results a number of PEG IFN + RBV studies have reported decrements in cognitive function (Fontana et al., 2007) and significantly less verbal IQs, perception and memory (Meguid & Moussa, 2010) during PEG IFN + RBV therapy and an improvement in cognitive function after treatment end (Fontana et al., 2007).

Other studies have reported mixed results. Fontana and colleagues (2002) reported a return to cognitive performance equal to controls for patients who achieved SVR. Kraus and
colleagues (2013) reported improvements compared to pre-treatment performance for those who achieved SVR. The Fontana and colleagues (2002), Fontana and colleagues (2007) and Kraus and colleagues (2013) did not report patient’s cognitive functions post treatment compared to normative means for either patients achieving SVR and patients who were non-responders.

The Hepatitis C Trust (2007) and the Hopwood (2009) qualitative studies reported significant numbers of patients who were experiencing ongoing cognitive dysfunction more than a year after treatment end despite the achieving of SVR. The Hepatitis C Trust (2007) found that 61% of patients were reporting cognitive function problems 6 months after treatment end and 35% were reporting cognitive function problems 12 months or longer after treatment end. While these two qualitative studies reported results supporting the current study, these studies did not objectively compare cognitive function post treatment to baseline.

**Patient satisfaction at end of treatment and at three-month follow-up**

The present study found there was no change in treatment satisfaction between any of the time points measured in the current study. While the level of dissatisfaction increased from baseline to treatment end and from treatment end to three-month follow-up there was no significant difference. At all time points the mean score on the PSQ-18 was below the normative mean score of 50.20. These findings are consistent with the Canadian Balfour and colleagues (2004) PEG IFN + RBV study which found around 50% of patients were satisfied with their treatment and there were no differences in baseline and follow-up satisfaction scores, although a greater proportion did report a better sense of satisfaction with their health care at 10 months’ follow-up to the initial visit.

It was found that there was no change in treatment satisfaction between any of the time points measured. While the level of dissatisfaction increased from baseline to treatment end and from treatment end to three-month follow-up there was no significant difference. At
all time points the mean score on the PSQ-18 was below the normative mean score of 50.20. A review of literature found no research studies on patient satisfaction on triple therapy over the time of treatment to compare these findings with. A study by Re and colleagues (2011) reported a correlation between contentment and compliance with triple therapy. Patients whose side effects were addressed by medical personnel and then were properly managed felt better and were more likely to adhere to the study group. Because of the onerous drug treatment with triple therapy patient treatment satisfaction is critical in order to maintain treatment adherence. This result indicates that despite impairment in all psychological symptoms from baseline to treatment end measured in this study and the continued impairment of QOL, fatigue and sleep disorders at three-months follow-up patients, overall were satisfied with their medical treatment.,

7.1.5 **COMPARISON OF PSYCHOLOGICAL SYMPTOMS BETWEEN TRIPLE THERAPY PATIENTS AND PEG IFN + RBV PATIENTS AT TREATMENT END AND AT THREE-MONTH FOLLOW-UP**

The present study hypothesised the impairment of psychological symptoms would be significantly greater for triple therapy patients than for PEG IFN + RBV therapy at end of treatment, but there would be no significant difference at three-month follow-up to treatment end.

The hypothesis that there would be a significantly greater impairment of psychological symptoms for triple therapy than for PEG IFN + RBV at treatment end was not supported by the present study. Only sleep disorders measured by the PSQI and tension and anxiety measured by the POMS Tension/Anxiety scale showed a significant impairment for triple therapy patients compared to PEG IFN + RBV patients at treatment end. Interestingly there is no significant difference in the HADS Anxiety scale at treatment end. At treatment end patients for both therapies would have knowledge of the success or not of their treatment.
This may contribute to there being no significant differences between most of the psychological symptoms measured. Also, by treatment end more patients had discontinued treatment for triple therapy compared to PEG IFN+ RBV.

However, the hypothesis that there would be no significant difference in the impairment of psychological symptoms between triple therapy and PEG IFN + RBV at three-month follow-up was supported. At three-month follow-up the only psychological symptom which showed a significantly greater impairment for triple therapy compared to PEG IFN + RBV was again tension and anxiety measured by the POMS Tension/Anxiety scale. Furthermore, there was no significant difference between the two studies in the HADS Anxiety scale at three-month follow-up

7.1.6 COMPARISON OF PEG IFN +RBV THERAPY AND TRIPLE THERAPY
PATIENTS NOT COMPLETING THERAPY AND PATIENTS ACHIEVING SVR

The present study hypothesised that compared to PEG IFN + RBV therapy (Study 1), triple therapy (Study 2) would have a higher percentage of patients who do not complete therapy, but would have a higher percentage of patients who achieve SVR for those patients who do complete therapy.

The findings of the present study confirmed the hypothesis. The present study showed a higher percentage of patients in triple therapy compared to PEG IFN +RBV therapy discontinued treatment. Furthermore, the percentage of patients who completed treatment and who achieved SVR for triple therapy was higher than the percentage of PEG IFN + RBV patients who completed treatment and achieved SVR.

Furthermore, previous research also supports this hypothesis. Previous research has shown that boceprevir added to PEG IFN +RBV improved SVR (Bacon et al., 2011; Poordad et al., 2011). Furthermore, previous studies have shown boceprevir-based triple therapy has
been shown to have a higher rate of adverse effects compared to PEG IFN + RBV and therefore lesser clinical tolerance (Lim et al., 2014).

It is suggested that while boceprevir-based triple therapy has an improved SVR for those who complete treatment, when compared to PEG IFN + RBV therapy, the increased adverse side effects of the addition of boceprevir to PEG IFN + RBV create a lesser clinical tolerance and thus an increase in patients not completing treatment.

7.1.7 COMPARISON OF PSYCHOLOGICAL SYMPTOMS BETWEEN BASELINE AND THREE-MONTH FOLLOW-UP OF PATIENTS ACHIEVING SVR AND NON-RESPONDERS

The present study hypothesised that compared to non-responders, patients who achieved SVR after being treated with PEG IFN + RBV therapy (Study 1) and triple therapy (Study 2) would report more improved psychological symptoms at three-month follow-up compared to pre-treatment (baseline).

The results of the present study showed mixed findings in both studies and did not support the hypothesis. There were insufficient numbers of patients to determine any meaningful conclusion on these results.

The results for PEG IFN +RBV (Study 1) showed at all 3 time periods patients who achieved SVR showed less impairment in all the psychological symptoms measured except for the ACE-R. However, the change from baseline to three-month follow-up showed mixed results. There was less impairment at three-month follow-up compared to baseline for non-responders than those patients achieving SVR for the following: QOL, FSS, POMS (Depression/Dejection scale, Confusion/Bewilderment scale, Tension/Anxiety scale, Vigour/Activity scale), HADS Depression scale, TMT-A, and ACE-R. There was less impairment at three-month follow-up compared to baseline for patients achieving SVR than non-responders for the following: PSQI, POMS (Total Mood Disturbance, Anger/Hostility scale, Fatigue/Inertia scale), HADS Anxiety scale, TMT Part B and PSQ-18).
The results for triple therapy (Study 2) showed at all 3 time periods patients who achieved SVR showed less impairment in all the psychological symptoms measured except for the ACE-R, TMT Part A and PSQ-18.

There was less impairment at three-month follow-up compared to baseline for non-responders than those patients achieving SVR for the following: POMS (Depression/Dejection scale, Confusion/Bewilderment scale, Vigour/Activity scale), HADS Depression and Anxiety scales, MT Part A, TMT Part B and PSQ-18). There was less impairment at three-month follow-up compared to baseline for patients achieving SVR than non-responders for the following: QOL, FSS, PSQI, POMS (Total Mood Disturbance, Anger/Hostility scale, Fatigue/Inertia scale, Tension/Anxiety scale), and ACE-R.

7.1.8 COMPARISON OF PSYCHOLOGICAL SYMPTOMS OF PEG IFN + RBV PATIENTS AND TRIPLE THERAPY PATIENTS ACHIEVING SVR TO NORMATIVE MEANS

The present study hypothesised that in both PEG IFN + RBV therapy and triple therapy at three-month follow-up to treatment end for patients achieving SVR, there will be an impairment of psychological symptoms compared to normative means.

The results of the present study confirm this hypothesis for fatigue, sleep disorders, mood state disturbances and cognitive function. However, the results show that QOL, depression, and anxiety are within the normal range for typical adults, but the scores are at the lower end of those normal ranges. Patient dissatisfaction was reported as below the normative mean.

Fatigue (FSS) mean scores for PEG IFN + RBV (Study 1) and triple therapy (Study 2) were both 4.95. This compares to a fatigue mean score for healthy adults of 2.30 and 4.50 for depression alone (without fatigue associated conditions) and 5.40 for clinically significant fatigue. Furthermore, the overall mean scores for sleep disorders, measured by the PSQI, for
PEG IFN + RBV (Study 1) and triple therapy (Study 2) were 7.76 and 8.05. The normative mean score for the PSQI measure is 2.67 ($SD = 1.70$). A mean score of 6.53 is the cut off for EDS. Patients for both treatments reported mean scores above that for EDS.

All the POMS scales for both studies showed mean scores below that of the normative mean. Interestingly the scales which include depression, dejection, tension, and anxiety which measure the same symptoms measured in the HADS measure are all above the normative mean. The POMS measure does not provide a range for any of the scales.

Also, in both studies the mean scores for the ACE-R, the TMT Part A and TMT Part B showed cognitive impairment compared to the normative mean. The present study found the average mean score in cognitive function in memory, verbal fluency, attention, speed, and mental flexibility remained lower at three-month follow-up than the normative mean.

The present study investigated the effect of patient treatment dissatisfaction on patients with HCV infection using the Patient Satisfaction Questionnaire (PSQ-18). Both study groups patients reported a level of treatment dissatisfaction which was lower than the normative mean. There have been no previous studies which have investigated the comparison of SVR outcomes to normative means in either PEG IFN + RBV nor triple therapy.

7.1.9 ANECDOTAL RESPONSES

During data collection as they were completing the standardised questionnaires a number of participants expressed feelings towards and provided anecdotes about their illness and their experiences during their treatment. These comments dealt with issues that concerned them but weren’t captured in the questionnaires. However, they are likely to be important to their wellbeing and are therefore worthy of discussion in this section. For instance, after completing the questionnaire, participants wished to talk at length about the effects of HCV and treatment. A common theme was that participants felt uncomfortable
talking to friends and relatives about their illness because of the social stigma of HCV. They talked about the common narrative that HCV was caused by the participant’s past injecting-drug use and therefore others perceived the illness was due to the participant’s own actions. Participants in general said they welcomed the opportunity to talk freely to the study investigator as they were not able to do so very often. One participant stated that ‘it was nice to talk to someone who knows about the illness’.

Some participants who did speak to friends or relatives reported that there was a common misconception that HCV was contagious. This misconception and the negative social stigma associated with HCV meant many patients did not want to talk to others about their illness and treatment. Interestingly, on average participants reported in the QOL questionnaire that the domains community and relatives did not change over the three time periods measured and for the boceprevir-based triple therapy study the domain Relatives was reported as not important. Participant’s relations between family and friends were mixed. Some patients said they had good support from friends and relatives, but some participants said they just wanted to be left alone.

Whilst on average participants reported being satisfied with their medical treatment a common comment was that therapy was ‘hard going’. One participant stated that the research nurses ‘expect us to jump through hoops’ during therapy. Interestingly, one participant mentioned that injecting during therapy produced flashbacks to their earlier days of injecting-drug use. Despite being satisfied with their medical treatment many participants commented that there was no support after treatment finished. One participant mentioned that they felt that ‘patients were left to their own devices’ at the end of treatment.

The QOL questionnaire included the domain Work. This domain overall was reported by participants as not being important to their QOL, and also had a low satisfaction rating compared to other QOL domains. Many participants reported that due to their illness-related
fatigue they were only able to maintain part time work. Therefore, lifestyle choices relating to employment to employment and career development were continuing to be affected by ongoing fatigue. One participant, realising he could not continue in his past occupation, which required some degree of physical work, enrolled in a course in the health-related sector and said he was looking forward to his new occupation.

7.2 THEORETICAL IMPLICATIONS OF STUDY FINDINGS

The biopsychosocial model takes into account all relevant determinants of health and supports the integration of biological, psychological and social factors in the treatment of a patient (Taylor, 2008). This model does not diminish the impact of biological factors, but contributes to a better understanding of the impact of psychosocial factors on health and creates a more holistic approach to the treatment of a patient (Havelka et al., 2009). A consideration of the biopsychosocial model is particularly pertinent when considering the wellbeing of HCV patients, as there is support for the view that patients with HCV may be unexpectedly more impaired in psychological health compared to their physiological health. In most chronic diseases physiological impairment is more pronounced than psychological impairment (Foster, 2009).

This study was a longitudinal study which investigated changes in a number of psychological symptoms between baseline, treatment end and three-month follow-up for patients undergoing PEG IFN + RBV therapy and boceprevir-based triple therapy. In the earlier section of the discussion, the findings for the 8 hypotheses have been considered in relation to the findings and the literature. Overall, an important finding was that a number of psychological symptoms did not improve at three-month follow-up compared to baseline. This was the case for patients who were non-responders and also for those patients achieving SVR. This may suggest that factors other than biological factors are contributing to ongoing issues which are negatively affecting the wellbeing of patients post HCV treatment.
Those patients in the study who achieved SVR were advised by the health professionals responsible for the HCV treatment, that their treatment has been successful. However, to report treatment as being successful on the basis of achieving SVR only addresses a patient’s biological health and wellbeing and does not address the patient’s psychological and social health and wellbeing. It is no longer sufficient for health professionals to state that a treatment is successful only in terms of treatments in terms of the effect on the biological symptoms of HCV. The consideration of the improvement in the patient’s overall psychological and social health and wellbeing is also necessary when determining the successfulness of treatment.

The study found that at three-month follow-up compared to baseline, patients reported more problems in QOL, fatigue, sleep disorders, total mood states, depression and anxiety. Overall patients reported significantly more fatigue and sleep disorders at three months follow-up compared to baseline. Furthermore, patients reported lower QOL, worse mood states and more depression and anxiety at three-month follow-up compared to baseline but the differences were not significant. At three-month follow up patients reported impaired satisfaction in the QOL domains Goals/Values, Play, Creativity and Love and also reported the following domains as being important: Goals/Values, Friends, Self-esteem, Health, Relatives and Play. In addition, the study found significant correlations at baseline between QOL, fatigue, sleep disorders, mood state disturbances, depression, anxiety, cognitive function.

A review of the results highlights that sleep disorders and associated fatigue were the two symptoms that were significantly impaired at three-month follow-up compared to baseline. Studies have shown that sleep disorders and associated fatigue can be caused by depression, anxiety and psychological stress. Also, sleep disorders and associated fatigue can be the result of negative QOL issues and mood states and poor lifestyle choices. Furthermore,
the biological factor of the biopsychosocial model attributes the cause of conditions such as sleep disorders and fatigue to biological determinants. However, the study findings show sleep disorders and associated fatigue were the two factors that were significantly worse at three-month follow-up compared to baseline. This finding may suggest that sleep disorders and associated fatigue factors are more than symptoms of psychological and social factors but can be seen to be problem disorders unto themselves. These findings also raise a number of issues for the patient and for recommended interventions.

The negative effects of sleep disorders are numerous. Sleep disorders have been shown to significantly worsen many biological, psychological and social problems. Furthermore, adequate sleep and is necessary for recovery from illness and for illness prevention. In addition, sleep disorders can decrease the effectiveness of treatments (National Alliance on Mental Illness, 2016).

Because of the significant correlation of sleep disorders and fatigue to not only QOL, but also to mood states, depression, anxiety and cognitive functioning, it may be speculated that ongoing sleep disorders and associated fatigue are contributing to the worsening of those later factors at three-month follow-up compared to baseline. Thus, consideration may have to be given on how sleep disorders and associated fatigue may be contributing to the impairment of satisfaction in QOL domains such as Goals and Values. The domain Goals and Values includes beliefs about what matters most in life and how a person should live both now and in the future.

Furthermore, sleep disorders and associated fatigue may be having a negative effect on a patient’s life style and social problems. In addition, there may be a negative impact on, and a reduction in, the interaction between, significant others, family, friends and social contacts. Relationship problems may be manifest in dysfunctional emotional reactivity and the inability to process emotional information. Furthermore, sleep disorders and associated
fatigue may be affecting QOL by limiting lifestyle choices and affecting job and academic pursuits.

The above discussion of the relationship between sleep disorders and associated fatigue, and other psychological and social factors supports the relevance of the biopsychosocial model which emphasises a holistic approach to the treatment of a patient. The following section of the discussion considers appropriate interventions for sleep disorders and associated fatigue.

7.3 INTERVENTIONS

Patients participating in this study reported ongoing problems with fatigue, sleep disorders and QOL. This was the case for both those achieving SVR and non-responders. Despite this, the research nurses of the hospitals who treated the participants reported there was limited follow-up treatment available for ongoing problems in fatigue, sleep and QOL. Those patients who reported ongoing issues were in many cases treated with anti-depressants. Since fatigue, sleep disorders and certain domains comprising QOL were reported at three-month follow-up at levels significantly above those at baseline, interventions tailored to the individual needs of the patient to address those issues are recommended.

There are a number of changes to a patient’s life after successful therapy that are often reflected in the patient’s QOL. Therefore, QOL outcomes are an important consideration in the assessment of treatment effectiveness. Much research has been conducted on how a patient adjusts from being healthy to a life with a chronic illness. Little, if any, research has been conducted on how a patient who has suffered from a chronic illness for many years adjusts to a life when physiological illness has been cured.

Interventions to assist with rehabilitation of the patient relating to psychological and social factors may be categorised into: supportive and symptomatic, psychological and pharmacological. A thorough discussion on pharmacological interventions is beyond the
scope of this thesis and such interventions should be discussed between the patient and the patient’s health clinician especially if medicine is prescribed during therapy. A brief description of other interventions to assist in ongoing fatigue, sleep disorders and poor QOL are described below.

7.3.1 SUPPORTIVE AND SYMPTOMATIC INTERVENTIONS

Supportive and symptomatic interventions include educating and counselling patients about the potential impact of the symptoms they report on their QOL and may include individual, family and group therapies. Interventions may also include counselling in relaxation, exercise and distraction.

With regard to fatigue and sleep disorders, interventions may include psycho-education. These sessions may include the assessment of fatigue and sleep problems, education about environmental stimuli, sleep hygiene, time management, nutrition, life style changes, exercise, relaxation, distraction and group, family and social support (see Appendix O) (Sockalingam, Abbey, Alosaimi, & Novak, 2010). Interventions could also include training and coaching in self-care strategies for managing fatigue and energy conservation and activity management.

Aspects of personal relationships include relationships with significant others where the significant other may have been the caregiver. The research findings of this study point to this role changing when the caregiving is no longer required and emotional distress occurring because of changes in family dynamics. Furthermore, research findings of this study point to patient with HCV in many cases removing themselves from social contact because of fatigue, feeling nauseous and social stigma. Individual, family and group therapy may be appropriate to address ongoing relationship problems with a significant other, family friends and social contacts. Some of the techniques involved with supportive and symptomatic interventions overlap with psychological interventions.
7.3.2  PSYCHOLOGICAL INTERVENTIONS FOR FATIGUE AND SLEEP

Fatigue, sleep disorders and QOL were reported as ongoing problems three-months post-treatment and can therefore be considered chronic issues; therefore, psychological interventions may be appropriate. Psychological interventions may include Cognitive Behaviour Therapy (CBT), mindfulness and Acceptance and Commitment (ACT) therapies.

CBT addresses distorted and dysfunctional cognitions that result in negative affective states and maladaptive behaviours. CBT identifies, evaluates, modifies and replaces distorted cognitions with more accurate and adaptive cognitions. Behavioural experiments are used to test out distorted predictors and correct them. Correcting distorted cognitions produces improvements in affect and behaviour. The desired outcome of CBT is initially a symptomatic improvement and subsequently functional improvement.

CBT as a psychological intervention has shown to help reduce fatigue in patients suffering from chronic fatigue syndrome, as well as helping patients suffering from sleep disorders by improving sleep quality (Morin et al., 2006). The behavioural aspect of CBT includes involving the patient in considering how their behaviour affects their sleep. This may involve the consideration of lifestyle changes, sleep hygiene education, stimulus control, sleep restriction and relaxation training. Furthermore, addressing how the patient thinks may affect their behaviour and improve sleep and fatigue (Sockalingam et al., 2010).

Mindfulness concentrates on assisting a patient’s emotional wellbeing through the use of meditation. Research has shown that mindfulness has various positive psychological effects (Keng, Smoski, & Robins, 2011). ACT uses both acceptance and mindfulness strategies and educates the patient to accept a situation, personality trait or emotion in order to assist in reducing avoidant coping strategies thus allowing the patient move forward towards a life that fits with the values they have identified. According to the model, increasing acceptance should precede the lessening of symptoms. ACT also aims to enhance
a patient’s commitment to making changes. It has been reported that ACT improved QOL in patients suffering from primary insomnia (Hertensrein et al., 2014).

The following section discusses the application of abovementioned CBT, Mindfulness and ACT interventions to the psychological impairments to QOL reported in this study.

7.3.3 Psychological Interventions and Quality of Life

Given the multiple facets of QOL, a combination of the interventions discussed above may be appropriate to address impairment. To address the many facets that affect QOL, any intervention that is instituted should not only address psychological issues, but should also provide practical and functional assistance to the patient to enable them to begin functioning as a “well person” rather than as a “sick person”. Some factors which affect QOL include; goals/values, self-esteem, creativity, personal relationships (significant other, friends, relatives, lover), social relationships and work.

This study found that there was significant impairment in satisfaction at three-month follow-up compared to baseline in the QOL domains: Goals/Values, Play, Creativity and Love. This study also found that four QOL domains, Goals/Values, Friends, Self-esteem and Health showed relatively higher importance ratings. The domain Goals/Values was the only QOL domain that patients reported a significantly impairment satisfaction rating and also a relatively higher importance rating.

The factors which include goal setting may be addressed using psychological interventions such as CBT, ACT and mindfulness. Without this help the patient could easily be trapped into a cycle of anxiety, low self-esteem, frustration, anger and depression. In particular, strategies using ACT teach patients to accept feelings and to defuse or create distance from the content of distressing thoughts by focusing mindfully on the process of thinking itself. This allows the patient to focus on goal-based actions that are in line with life values and promotes mental and physical health and wellbeing.
CBT may be of assistance with relationship and employment issues. CBT has been shown to have a significant effect on the total score of QOL of cardiovascular patients. In that study the three domains; emotional, social and physical functioning of the MacNew QOL questionnaire (Valentini, Lim, Heller, & Knapp, 1996) all showed significant improvement following CBT training (Nekouei, Yousefy, & Manshaee, 2012).

ACT and mindfulness interventions including life skills coaching may be appropriate where the patient wishes to return to work and finds that their job skills may be obsolete. Interventions may involve the patient learning to accept what they may not be able to do and to redirect the patient to ‘think outside the square’, According to the model, increasing acceptance should precede the lessening of symptoms.

7.4 CONTRIBUTIONS TO RESEARCH

The present study is based on a health psychology perspective, with an emphasis on the role that the biopsychosocial model plays in illness and in health. This approach is appropriate as research has shown the HCV-infected population are more impaired in mental health than in physical health when compared to other chronic illnesses. Therefore, the present study has used the QOLI measure, with the emphasis on psychological and sociopsychological domains, and patient’s satisfaction and importance ratings to measure QOL instead of the SF-36 which emphasises functional abilities or impairment to measure health related quality of life.

Thus, the present study extends current research in a notable way by identifying the psychological and sociopsychological symptoms affecting the impairment of QOL of the HCV-infected patient over the term of treatment with PEG IFN + RBV therapy and triple therapy and three-month follow-up to treatment end. To the best knowledge of the researcher the present study is the first to use the QOLI in the research of HCV therapy. HCV research
to date has nearly exclusively used the SF-36 measure and therefore findings have been limited to functional abilities and impairment.

Furthermore, to the best knowledge of the researcher, the present study is the first to compare QOL symptoms of PEG IFN + RBV with the QOL symptoms of triple therapy at treatment end and at three-month post treatment end. Thus, the present study is the first study to identify any psychological differences between the two studies that were affecting changes in QOL during and after PEG IFN + RBV therapy and triple therapy.

Anecdotal reports and prior PEG IFN + RBV quantitative studies have shown fatigue has severe effects on HCV-infected patients. Despite this, there are gaps in research on fatigue and PEG IFN + RBV therapy and triple therapy. The benefit of the present study from a quantitative study perspective was the use of a fatigue specific measure instead of the generic SF-36, Vitality scale in the study of fatigue. Also, at the time of writing and to the best knowledge of the researcher, there have been no studies which have investigated fatigue in patients achieving SVR and non-responders at three-month follow-up to treatment end using a fatigue specific measure.

The results of research into fatigue after treatment end have been reported in two qualitative studies (Hopwood, 2009; The Hepatitis C Trust, 2007). The two qualitative studies were limited by using web-based questionnaires (The Hepatitis C Trust, 2007) and using face-to-face and telephone interviewing (Hopwood, 2009). Furthermore, the advantage of the current study’s use of quantitative methodology was the ability to determine objectively that there was a significantly greater level of fatigue reported at three-month post-treatment compared to the level of reported sleep disorders at baseline.

The present study also extends current research in measuring fatigue for boceprevir-based triple therapy at treatment end and three-months post therapy. A review of literature found no prior research on fatigue for boceprevir-based triple therapy at treatment end nor at
any follow-up period. However, one study found up to 60% of triple therapy patients reported fatigue during boceprevir-based triple therapy (Poordad et al., 2011).

At the time of writing, to the best knowledge of the researcher, there were no studies which had investigated fatigue for patients achieving SVR and non-responders at three-month follow-up for boceprevir-based triple therapy. The Younossi and colleagues (2014a) study, while not investigating boceprevir-based triple therapy did investigate SOF-based triple therapy.

Sleep is important for both psychological and physiological health. Sleep disorders and PEG IFN + RBV therapy been reported in two qualitative studies (Hopwood, 2009; The Hepatitis C Trust, 2007). Similar to the investigation of fatigue, the two qualitative studies were limited by using web-based questionnaires and face-to-face interviews. Furthermore, the advantage of the current study’s use of quantitative methodology was the ability to determine objectively that there was a significantly greater level of sleep disorders reported at three-month post-treatment compared to the level of reported sleep disorders at baseline.

The present study is the first quantitative study to investigate sleep disorders in both PEG IFN + RBV and boceprevir-based triple therapies at treatment end and three-month post treatment. The present study is also the first quantitative study to investigate and report sleep disorders in SVR and non-responders post therapy at treatment end and three-month post treatment. Thus, the present study adds to current research by reporting on gaps in current research in sleep disorders and HCV, PEG IFN + RBV therapy and triple therapy.

Previous research on reported depression after treatment end is limited. Previous research on depression and HCV and during PEG IFN + RBV is well documented. However, a review of the literature found no data on the patient reports of depression for PEG IFN + RBV therapy at the three-month post treatment period and SVR, although ongoing depression after PEG IFN + RBV therapy have been reported in two qualitative studies.
Kow and colleagues (2010) reported that depression was one of the common psychological adverse events reported by patients as the reason for withdrawal from triple therapy. A review of the literature found no studies which had specifically investigated the relationship between depression, triple therapy, and post treatment outcomes, and SVR. Thus, the present study adds to current research by using qualitative reporting on PEG IFN + RBV therapy post treatment, and SVR. Furthermore, the present study adds to current research by reporting on depression, post treatment outcomes and SVR in triple therapy.

The present study adds to the current literature by using objective quantitative measures to investigate gaps in research in cognitive function post treatment and SVR for patients undergoing PEG IFN + RBV therapy. Also, a review of the literature revealed no previous studies which have researched cognitive function during triple therapy nor post treatment triple therapy. Thus, the present study adds further to the current literature by reporting on cognitive function for PEG IFN + RBV post treatment and during triple therapy and three-month post treatment for triple therapy. By using ACE-R and TMT Trial A and TMT Trial B the present study was able to identify impairment to verbal fluency, memory and those cognitive skills requiring concentration by the patient.

7.5 LIMITATIONS

The present study had some limitations. The primary limitation of the present study was the small sample size. Only 52 participants (25 PEG IFN + RBV therapy group, 27 Triple therapy group) completed the study in the three-month follow-up to treatment end questionnaire Therefore, the results should be considered hypothesis-generating and further evaluation in a larger population is warranted. Again, there may have been sample bias because the discontinuance of therapy may have been because of depression, fatigue, or adverse physiological side effects of therapy. However, the patients who did complete the studies and patients who withdrew were similar with respect to their demographic values. The
results were obtained from patients who received care at two primary care sites that might not be representative of most primary care sites in other parts of the country. Another limitation of the study was the lack of a control group.

Because the present study was carried out within the clinical environment, there were several aspects which were not controlled for. Some patients did not attend their final treatment and three-month treatment follow-up clinic appointments when scheduled. This meant the treatment date and three-month treatment end follow-up was not able to be precisely controlled. The study was based on a single period from baseline to treatment end and changes may have occurred at varying times during that time period. Previous studies have used a number of follow-up periods (Loftis et al., 2004; Raison et al., 2005a; Raison et al., 2005b). Also, because information was collected at single points in time, and some patients were interviewed at their clinic, some at their homes, and some took parts of the questionnaire home and returned to the researcher by mail confounding factors may not have been distributed equally among the patients. However, many of the differences and associations reported in the study, as well as the lack of those, are observed consistently in different studies, and match with prior knowledge about the effect of HCV therapies.

The present study reported the use of antidepressants for both therapies at baseline, however the administration of antidepressants during treatment was not monitored by the researcher. Because the prescribing of antidepressants during and for the 3-month follow-up period was not systematically recorded the lack of a contribution of these agents to treatment outcomes and psychological symptoms cannot be determined. A number of earlier studies have shown that antidepressants reduced depression in PEG IFN + RBV treatment (Raison et al., 2005a).

Another methodological limitation of the present study was the use of self-report measures which are subject to response bias. However, this type of data collection is the case
in all studies evolving the evaluation of symptoms that have no objective measures and remains the only practical way to assess many of the elements examined in the present study.

Data was not collected on whether the patients in either therapies were treatment naïve or treatment experienced. Whether a patient was treatment naïve or treatment experienced may have affected any of the psychological symptoms measured and the SVR in either therapy.

A number of these limitations related to issues between subjects. The present study was a prospective, repeated measures design evaluating patients at baseline, treatment end and three-months follow-up and therefore do not affect the overall results of the present study. Furthermore, despite these limitations, the present study suggests that QOL, sleep disorders, and fatigue should be given greater attention in both clinical work and research on psychotherapy during and after HCV therapy. The present study points the way for additional research on these important psychological symptoms.

7.6 CONCLUSIONS

7.6.1. GENERAL DISCUSSION

For both therapies, to varying degrees, all of the patients reported impairment to all of the psychological symptoms at three-month follow-up, compared to baseline, despite achieving SVR. It is important to identify the most significant of these impairments to enable specific treatment and interventions.

These findings are of course overall mean scores and within those results are patients who are suffering well above the mean and some below. Depression is commonly treated with pharmacological intervention with antidepressants or with psychological and behavioural interventions such as Cognitive Behavioural Therapy (CBT). However, based on an analysis of the results of the present study and a review of previous research, the two significant psychological symptoms that are neglected and require treatment are fatigue and
sleep disorders. For both therapies fatigue and sleep problems were reported by patients as being higher than normative scores at baseline, treatment end and at 3-month follow-up. These two psychological symptoms have not been well researched in HCV post treatment care despite reports such as the Hepatitis C Trust (2007) survey reporting fatigue in 57% of patients up to 6- and 12-months post HCV treatment. The majority of HCV research to date has concentrated on HRQL, with the emphasis on functional abilities and impairment, and depression to the detriment of other psychological symptoms. Therefore, in addition to existing interventions which are in place to address depression, it is recommended that interventions be instituted for up to 12 months post treatment to separately address fatigue and sleep problems.

The other issue requiring attention, which is highlighted in the present study, is QOL. Are there factors comprising QOL which are affecting the patient’s post treatment psychological wellbeing that are not being addressed by clinicians? Studies have shown that persons infected with HCV have more psychological symptoms that patients with other chronic illnesses. QOL comprises many factors which the patient was asked to consider when answering the QOLI questionnaire. The QOLI measures domains such as self-esteem, goals and values, work, play, relationships, and community and how satisfied the patient is with these domains and how important these domains are to the patient. The results of that measure reveal a mean at the lower end of the normative mean for QOL. The results also indicate a significant impairment of QOL at three-month follow-up compared to baseline. This is the case for both therapies.

The SF-36 which to date has been used in the substantially all studies involving HCV and HCV therapies measures health related quality of life (HRQL) with the emphasis on functional abilities and impairments. With a prospective longitudinal, repeated measures study such as this study, the QOLI is able to identify relatively those domains which affect
QOL changes over time, those domains that have relatively the greater effect on QOL over time, those domains the patient are most and least satisfied with, and how important those domains are to the patient. This study showed that 9 of the 16 domains in the QOLI; Health, Self-esteeom, Goals and Values, Play, Learning, Creativity, Helping, Love, and Friends effected changes in QOL over time, while the domains; Money, Work, Children, Relatives, Home, Neighbourhood, and Community did not. Furthermore, there were significant impairment of patient satisfaction at three-month follow-up compared to baseline with the domains; Goals and Values, Play, Creativity and Love, and of those four domains Goals had a relatively high importance rating. Thus, the QOLI results for this study identified Goals and Values as being a domain that overall patients reported as being impaired but which was also relatively important. The domain Goals and Values are defined as: Beliefs about what matters most in life and how a patient should live, both now and in the future. This includes goals in life, what a patient thinks is right or wrong, and the purpose or meaning of life as the patient sees it. Also, the QOLI was able to identify the 9 domains that were affected changed on the QOL over time. These results enable the clinician to direct interventions to specific psychological symptoms that are impaired.

Based on the research that the HCV population is more mentally impaired than physically impaired when compared to other chronically ill populations, it is suggested that a measure such as the QOLI would be a more appropriate measure to use by clinicians to enable the identification of specific psychological impairments rather than the SF-36 with the emphasis on functional abilities and impairment.

7.6.2 CONCLUSION

The present study has investigated HCV and PEG IFN + RBV and triple therapy, over time, from a health psychology perspective. Health psychology purports that biological,
psychological, and social factors all play a significant role in illness and health. The experience of HCV and HCV therapies causes psychological consequences and necessitates adjustment in multiple life domains. The results of this research show that all the psychological symptoms measured were significantly impaired by HCV therapy and even at three-month follow-up QOL, fatigue for both PEG IFN+ RBV and triple therapy and sleep disorders for triple therapy were significantly impaired compared to baseline.

The QOL results of this study are in contrast to a number of previous HCV studies which have used the SF-36, which have shown improvement in HRQL after treatment end compared to baseline. The present study using the QOLI to measure QOL shows no such improvement. These results may support the suggestion that QOL with the emphasis on life satisfaction can either improve or be impaired without changes in functional abilities or impairment (Diener & Seligman, 2004; Frisch et al., 2005). This may also explain anecdotal reports that patients are still feeling unwell some months after achieving SVR.

Fatigue is a complex symptom and can be influenced by a number of sources including insomnia, anaemia, poor diet and an individual’s medical history and lifestyle choices. The impact of these aspects separately cannot be determined from this analysis and requires additional study. The analysis of the current study provides evidence that patients treated with PEG IFN + RBV and boceprevir-based triple therapy have significant increases in fatigue at treatment end compared to baseline. While the reported mean score for fatigue is reduced at three-month follow-up compared to treatment end, the reported mean score at three-month follow-up was significantly higher than at baseline. In fact, for both therapies and for those achieving SVR-12 and non-responders, the FSS mean score was above the normative mean score for healthy adults and above the score indicating fatigue and depression alone. Furthermore, even after SVR at three-month follow-up to HCV treatment end, those patients in both therapy study groups were still reporting significantly higher
fatigue mean scores than at baseline. It is important that fatigue be identified separately from other psychological symptoms such as depression to enable appropriate intervention.

The study also found impaired sleep disorders at three-month follow-up compared to baseline, although the difference was only significant for triple therapy. A review of the literature revealed two quantitative studies which have investigated sleep disorders post HCV therapy. Also, the review indicated that sleep disorders involving HCV therapy has been neglected despite studies reporting significant sleep disorders in patients with HCV-infection. Sleep disorders can be manifest in different symptoms and are classified into 8 categories by The American Academy of Sleep Medicine. Sleep disorders may be a cause or symptom of depression and affects a patient’s QOL and level of fatigue. Therefore, the importance of sleep disorders in HCV therapy must not be overlooked and should be addressed separately from depression and fatigue by the clinician.

Psychological symptoms impact on treatment compliance, subsequent functional loss and patient’s overall diagnosis and QOL. Therefore, diagnosing these impairments is critical for the successful treatment of a HCV-infected patient. HCV is predicted to be a significant problem both worldwide and in New Zealand. However, current treatments and follow-up of psychological care have significant shortcomings. Therefore, consideration of future strategies in prevention, treatment and follow-up care is warranted.

In conclusion, whether a patient has recovered from HCV should consider not only physiological measures such as SVR, but must also include the psychological health and wellbeing of the patient. If the patient is reporting ongoing psychological impairment despite achieving SVR then one cannot conclude the patient has completely recovered from HCV.

**7.7 Future Research**

The present study found, that for both patients achieving SVR and non-responders, at three-month follow-up, QOL, fatigue, and sleep disorders did not return to baseline. The
results of the present study also indicated that fatigue and sleep disorders at three-month follow-up were significantly impaired compared to normative means and also indicated QOL neared the lower range of the norm for healthy adults. Therefore, future research should concentrate on these symptoms. Since studies have shown that patients with HCV infection are more likely to have impaired mental health compared to patients with other chronic illness it is suggested that even with newer DAA therapies and interferon-free and ribavirin-free therapies patients may still suffer impaired QOL following treatment end, even though patients may achieve SVR.

Using the QOLI, this study was able to identify the psychological and sociopsychological domains which affected QOL over time, and those domains that did not. Therefore, it is suggested that patients complete the QOLI measure at treatment end and at three-month follow-up to identify possible ongoing impaired psychological and sociopsychological domains in order to enhance the accuracy of clinical interventions. Also, it is suggested that any assessment of future HCV therapies also include the QOLI measure in order to identify the psychological and sociopsychological effects of therapies.

According to research, fatigue remains one of the least understood and neglected symptoms by health professionals and is often misdiagnosed as depression. The results of the present study showed that fatigue was not only significantly more impaired at three-month follow-up than at baseline and but was also more impaired than the normative mean. Therefore, is suggested that future research involving clinical assessments and interventions of HCV patients and any assessments of future therapies include a specific measure for fatigue such as the FSS in order to assist in the differentiation between fatigue and other psychological symptoms such as depression.

This study reported that the mean for sleep disorders at three-month follow-up were more impaired than at baseline and in the case of triple therapy that impairment was
significant. Also, for both therapies sleep disorders at three-month follow-up were more impaired than the normative mean for many serious sleep disorders. Sleep disorders in HCV population have not been well researched. However, sleep disorders can negatively affect physical and mental health. Sleep disorders have been classified into 8 categories and thus highlights that sleep disorders are complex. Therefore, existing HCV therapies and new HCV therapies as they are introduced, should be researched to record the effect on sleep. That research should be investigated with a measure such as the PSQI which specifically measures sleep disorders.

Future research on the effects on the brain of HCV infection, HCV therapy, both during and post therapy, may deliver important data on the nature of sleep disorders in HCV patients. Furthermore, research into the nature of sleep disorder, both physiological and psychosocial, would provide important information on the course of HCV disease, aid in better adherence to therapy and allow for appropriate supportive care.

Because of the preponderance of psychological and sociopsychological symptoms in the HCV population there is scope for qualitative research relating to HCV and HCV therapies. Examples of questions that could be the basis for future qualitative research are; How does a person who has been physically sick for many years and is now being told he or she is cured cope with life? How does a person manage getting back into the workforce after possibly being sick for many years when their work skills may now be obsolete? How does a person manage relationships, particularly with significant others after being sick for many years?

The present study approached the topic of the relationship between psychological symptoms and HCV, PEG IFN +RBV and triple therapy from a health psychology perspective. However, there were a number of aspects of health psychology which were not covered in this study which would benefit from future research with HCV and HCV therapy.
These include the relationship with: Illness perceptions, mindfulness, benefit finding (finding positive meaning in an illness), positive and negative affect, positive adjustment, coping processes, non-pharmacological pain management, and effects of caregivers. This list is indicative of the topics which may be relevant in research involving HCV and HCV therapy.

Rabin and colleagues (2004) quantitative study of cancer patient’s illness perceptions is an example of a study from a health psychology perspective which could be used for future HCV research. Using HADS and Fear of Recurrence measures, it was found that individuals who viewed their cancer as chronic evidenced greater distress than those who conceptualized their cancer as acute. Another example of a study from a health psychology perspective which is applicable to future HCV research involved cancer patients and mindfulness. It was found that women breast cancer survivors who used mindfulness-based stress reduction (MBSR) reported significant improvements in scores for distress, symptom burden, coping capacity, and mental health compared to a control group compared to a control group who did not use MBSR. The study used HADS, Memorial Symptom Assessment Scale, SF-36, Sense of Coherence, Mindfulness Questionnaire, and Posttraumatic Growth Index (Sarenmalm, Martensson, Andersson, Karlsson, & Bergh, 2017).


Everson, G T, Sims, K D, & Thuluvath, P J. (2013b). Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks on treatment-naive patients with chronic HCV genotype 1 infection Hepatology, 58, LB-1.


Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine, 6(2), 97-111.


### APPENDIX A

**SIDE EFFECTS OF PEGYLATED INTERFERON (PEG IFN)**

*(PEGASYS) (Roche, 2009b)*

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychological</strong></td>
<td>Depression is commonly reported by patients. Suicidal ideation, attempted suicide, anxiety, irritability, aggressive behaviour, confusion, alteration of mental status and psychosis have also been reported in some patients being treated with Pegasys. It is recommended that Pegasys treatment be discontinued where psychiatric symptoms persist or worsen and in particular where suicidal ideation is identified (The literature on psychological side effects will be discussed in Chapter 3).</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>Infections including upper respiratory infection, bronchitis, pneumonia, oral candidiasis, herpes simplex, fungal viral and bacterial infections have all been reported by patients.</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td>Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have all been side effects reported with interferon alpha therapies. Patient’s being treated with Pegasys are recommended to have an electrocardiogram before commencing Pegasys treatment and if there is any deterioration in cardiovascular status it is recommended that treatment be discontinued or suspended.</td>
</tr>
<tr>
<td><strong>Endocrine system</strong></td>
<td>Roche recommend that treatment be discontinued or suspended if endocrine or induction to autoimmunity problems occur.</td>
</tr>
<tr>
<td><strong>Induction to autoimmunity</strong></td>
<td></td>
</tr>
</tbody>
</table>
Blood and lymphatic system

Disorders

Roche recommend that if blood and lymphatic system disorders occur then treatment is to be suspended.

Neurological

Roche suggest that if blood and lymphatic system disorders occur then treatment is to be suspended.

Liver function

Some patients may suffer hepatic decompensation in which case it is recommended that treatment be discontinued. When the increase in ALT levels becomes progressive and clinically significant despite dose reduction, it is recommended that treatment be discontinued.

Ocular changes

Retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, neuropathy and retinal artery or vein obstruction, which may result in the loss of sight, have all been reported as side effects of Pegasys. It is recommended that patients who develop new or worsening ophthalmologic symptoms then treatment should be discontinued.

Skin disorders

Psoriasis and sarcoid may be exacerbated or provoked by the use of alpha interferons. It is recommended that treatment be discontinued with the onset or worsening of psoriatic lesions.

Dental/ Periodontal disorders

There have been reported cases of dental and periodontal disorders, which may lead to loss of teeth in patients receiving pegylated interferon alpha and ribavirin treatment. Also, long term treatment with Pegasys and ribavirin may cause dry mouth which can damage teeth and the muscle membranes of the mouth.
## APPENDIX B

### SIDE EFFECTS OF RIBAVIRIN  (Roche, 2009c)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematological</strong></td>
<td>Haemolytic anaemia has been reported as a side effect of ribavirin. Patients with haemolytic anaemia may require dose reduction or discontinuation of ribavirin (Loustaud-Rati, Rousseau, Marquet, Denis, &amp; Alain, 2009). Anaemia can occur in 36% of patients. In 20% of patients the haemoglobin level drops below 10g/dl and in 5% of patients it drops below 8.5 g/dl (Gaeta et al., 2008). The drop in haemoglobin levels is because the ribavirin metabolite, ribavirin triphosphate accumulates in red blood cells at 60 times the plasma causing haemolysis (De Franceschi et al., 2000).</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Respiratory problems including coughs, breathlessness, pharyngitis and sinusitis have been reported as side effects.</td>
</tr>
<tr>
<td><strong>Embryonic development</strong></td>
<td>It has been reported that ribavirin may cause birth defects. Women who are pregnant or who are contemplating pregnancy and the spouses of women who are contemplating pregnancy during treatment were excluded from treatment at the hospitals in which this study was conducted.</td>
</tr>
</tbody>
</table>
Other side effects

Other side effects include worsening liver functioning, rash and itching, severe muscle cramps, hair loss, fatigue, sweating and headaches.
APPENDIX C

CRITERIA FOR PHARMAC FUNDING OF PEG IFN + RBV

On 9 March 2009 PHARMAC announced the approval of the funding of pegylated interferon plus ribavirin for chronic HCV patients, effective from 1 April 2009 with the following criteria (PHARMAC, 2009, p.2):

Initial application – (genotype 1, 4, 5, and 6 infection or co-infection with HIV)) from any specialists. Approvals are valid for 48 months for applications meeting the following criteria:

1. Patient has chronic hepatitis C, genotype 1, 4, 5 or 6 infection; or
2. Patient has chronic hepatitis C and is co-infected with HIV.

Note: Consider stopping treatment if serum HCV RNA level at week 12 remains detectable by PCR and has not reduced by at least 2 logs from the baseline level as this is predictive of treatment failure.

Note: Consider reducing treatment to 24 weeks if serum HCV RNA level at Week 4 is undetectable by sensitive PCR assay (< 50IU/mL) and baseline serum HCV RNA is <400,000 IU/mL.

Initial application- (genotype 2 or 3 infection without co-infection with HIV) from any specialist. Approvals valid for 6 months for applications where the patient has chronic hepatitis C, genotype 2 or 3 infection.

PHARMAC amended the funding criteria of PEG IFN + RBV therapy from 1 September 2013. The PHARMAC notification listed the following restrictions on the availability of funded PEG IFN + RBV treatment from 1 September 2013 (PHARMAC, 2013, p.3-4)
Initial application – (chronic hepatitis C- genotype 1, 4, 5, or 6 infection or co-infection with HIV or genotype 2 or 3 post liver transplant) from any specialist. Approvals are valid for 18 months for applications meeting the following criteria:

Both

1. All of the following:
   1.1 Patient has chronic hepatitis C, genotype 1, 4, 5 or 6 infection; or
   1.2 Patient has chronic hepatitis C and is co-infected with HIV; or
   1.3 Patient has chronic hepatitis C, genotype 2 or 3 and has received a liver transplant; and

2. Maximum of 48 weeks therapy.

Notes:

Consider stopping treatment if there is an absence of a virological response (defined as at least a 2-log reduction in viral load) following 12 weeks of treatment since this is predictive of treatment failure.

Consider reducing treatment to 24 weeks if serum HCV RNA level at Week 4 is undetectable by sensitive PCR assay (less than 50IU/ mL) and baseline serum HCV RNA is less than 400,000 IU/ mL.

Renewal application – (chronic hepatitis C- genotype 1, infection) from gastroenterologist, infectious disease physician or general physician. Approvals are valid for 18 months for applications meeting the following criteria:

All of the following:

1. Patient has chronic hepatitis C, genotype 1 and

2. Patient has had previous treatment with pegylated interferon treatment; and

3. Either:
   3.1 Patient has responder relapsed; or
3.2 Patient was a partial responder; and

4 Patient is to be treated in combination with boceprevir; and

5 Maximum of 48 weeks therapy.

Initial application – (chronic hepatitis C- genotype 1 infection treatment more than 4 years approval) from gastroenterologist, infectious disease physician or general physician.

Approvals are valid for 18 months for applications meeting the following criteria:

All of the following:

1 Patient has chronic hepatitis C, genotype 1 and

2 Patient has had previous treatment with PEG IFN + RBV; and

3 Either:
   3.1 Patient has responder relapsed; or
   3.2 Patient was a partial responder; or
   3.3 Patient received pegylated interferon prior to 2004; and

4 Patient is to be treated in combination with boceprevir; and

5 Maximum of 48 weeks therapy.

Initial application – (chronic hepatitis C- genotype 2 or 3 infection without co-infection with HIV) from any specialist. Approvals are valid for 12 months for applications meeting the following criteria:

Both:

1 Patient has chronic hepatitis C, genotype 2 and 3 infection; and

2 Maximum of 6-month therapy.
APPENDIX D

CRITERIA FOR PHARMAC FUNDING OF TRIPLE THERAPY

PHARMAC announced on 9 August 2013 the approval of the funding of triple therapy boceprevir from 1 September 2013 (PHARMAC, 2013) (see Table 2.3). The PHARMAC notification listed the following restrictions on the availability of funded boceprevir triple therapy (PHARMAC, 2013, p.2):

Initial application – (chronic hepatitis C - genotype 1, first-line) from gastroenterologist, infectious disease physician or general physician. Approvals are valid for 18 months for applications meeting the following criteria:

All of the following:

1. Patient has chronic hepatitis C, genotype 1 and
2. Patient has not received prior pegylated interferon treatment; and
3. Patient has IL28 genotype CT or TT allele; and
4. Patient is to be treated in combination with PEG IFN + RBV; and
5. Patient is hepatitis C protease inhibitor treatment-naïve; and
6. Maximum of 44 weeks therapy.

Initial application – (chronic hepatitis C - genotype 1, second-line) from gastroenterologist, infectious disease physician or general physician. Approvals are valid for 18 months for applications meeting the following criteria:

All of the following:

1. Patient has chronic hepatitis C, genotype 1 and
2. Patient has received pegylated interferon treatment; and
3. Any one of:
   - Patient was a responder relapse; or
- Patient was a partial responder; or
- Patient received pegylated interferon prior to 2004; and

4 Patient is to be treated in combination with PEG IFN + RBV; and

5 Maximum of 44 weeks therapy.
## APPENDIX E

### SUMMARY OF PHARMAC FUNDING OF HCV TREATMENT IN NZ

<table>
<thead>
<tr>
<th>Date</th>
<th>Generic Name</th>
<th>Brand (Manufacturer)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 April, 2009</td>
<td>PEG IF + RBV</td>
<td>Pegasys and Copegus (Roche)</td>
<td>Approved funds for treatment for patients with HCV genotypes 1, 4, 5 and 6, or HCV with HIV co-infection for 48 weeks. Treatment for HCV genotype 2 and 3 funded for 24 weeks.</td>
</tr>
<tr>
<td>1 September, 2013</td>
<td>Boceprevir</td>
<td>Victrelis (Merck &amp; Co)</td>
<td>Approved funding from 1 September 2013 until 30 June, 2016. Approved further Pegasys funding until 30 June 2017,</td>
</tr>
<tr>
<td>10 August, 2015</td>
<td>DAAs</td>
<td></td>
<td>Request for Information-Hepatitis C Treatments. To supply Classes of DAAs including: Non-structural protein (NS) 3/4A protease inhibitors NS5A inhibitors NS5B nucleoside polymerase inhibitors NS5B non-nucleoside polymerase inhibitors</td>
</tr>
</tbody>
</table>
### APPENDIX F

**PHARMAC PRICE AND SUBSIDY**

**FROM 1ST SEPTEMBER 2013 (PHARMAC, 2013)**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Presentation</th>
<th>Brand</th>
<th>Pack size</th>
<th>Price and subsidy NZS(ex GST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon alfa 2a</td>
<td>Inj 180 mcg prefilled syringe (2162806)</td>
<td>Pegasys</td>
<td>4</td>
<td>$900.00</td>
</tr>
<tr>
<td>Pegylated interferon alfa 2a</td>
<td>Inj 180 mcg prefilled syringe x 4 with ribavirin tab 200 mg x 112 (2190117)</td>
<td>Pegasys</td>
<td>1 OP</td>
<td>$1,159.84</td>
</tr>
<tr>
<td>Pegylated interferon alfa 2a</td>
<td>Inj 180 mcg prefilled syringe x 4 with ribavirin tab 200 mg x 168 (2190087)</td>
<td>Pegasys</td>
<td>1 OP</td>
<td>$1,290.00</td>
</tr>
<tr>
<td>Pegylated interferon alfa 2a</td>
<td>Inj 135 mcg prefilled syringe x 4 with ribavirin tab 200 mg x 168 (2190109)</td>
<td>Pegasys</td>
<td>1 OP</td>
<td>$1,975.00</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Capsule</td>
<td>Victrelis</td>
<td>336</td>
<td>$5,015.00</td>
</tr>
</tbody>
</table>
## APPENDIX G

### COSTS TO PHARMAC FOR PEG IFN + RBV AND TRIPLE THERAPY DRUGS

1ST SEPTEMBER 2013 (PHARMAC, 2013).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost NZ$(ex GST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon plus ribavirin:</td>
<td></td>
</tr>
<tr>
<td>24 week treatment</td>
<td>$11,850.00</td>
</tr>
<tr>
<td>48 week treatment</td>
<td>$23,700.00</td>
</tr>
<tr>
<td>Triple therapy:</td>
<td></td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td>$78,865.00</td>
</tr>
<tr>
<td>Naïve non-cirrhotic patients</td>
<td></td>
</tr>
<tr>
<td>RVR</td>
<td>$43,915.00</td>
</tr>
<tr>
<td>No RVR</td>
<td>$56,752.00</td>
</tr>
<tr>
<td>Treatment experienced (partial responders/relapsers)</td>
<td></td>
</tr>
<tr>
<td>RVR</td>
<td>$57,900.00</td>
</tr>
<tr>
<td>No RVR</td>
<td>$64,319.00</td>
</tr>
</tbody>
</table>
## APPENDIX H

### CLASSES OF FIRST AND SECOND GENERATION DAAs

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS3A/4B inhibitors</strong></td>
<td>Boceprevir</td>
<td>Victrelis</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Telaprevir</td>
<td>Invicek</td>
<td>Approved</td>
</tr>
<tr>
<td>(NS3/NS4A serine</td>
<td>Asunaprevir</td>
<td>Sunvepra</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>protease inhibitors)</td>
<td>Faldaprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Danoprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simeprevir</td>
<td>Olysio</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>ABT-450</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paritaprevir</td>
<td>Viekira Pak</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Norvir/Viekira Pak</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Cyclophilin inhibitors</strong></td>
<td>Alisoporivir</td>
<td>Debio-025</td>
<td></td>
</tr>
<tr>
<td><strong>NS5B polymerase</strong></td>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>Approved</td>
</tr>
<tr>
<td>nucleoside inhibitors</td>
<td>Mericitabire</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABT-333</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NS5B3 polymerase</strong></td>
<td>VX-222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside</td>
<td>BMS-791325</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dasabuvir</td>
<td>Viekira Pak</td>
<td>Approved</td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>Ombitasvir</td>
<td>Viekira Pak</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>ABT-267</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is CYP3A a cyclophilin
### APPENDIX I

**FDA APPROVED TREATMENTS FOR HCV**

**AS AT 31st DECEMBER 2015**

<table>
<thead>
<tr>
<th>Date</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 1997</td>
<td>Interferon</td>
<td>Infergen</td>
<td>Approved for treatment of persons with chronic HCV</td>
</tr>
<tr>
<td>Aphacon-1</td>
<td>(Amgen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 2001</td>
<td>Pegylated</td>
<td>Pegintron</td>
<td>Approved in combination with ribavirin for persons over 3 years of age with</td>
</tr>
<tr>
<td>interferon</td>
<td>alpha-2b</td>
<td>(Schering Plough)</td>
<td>compensated liver disease and alone for persons with compensated liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>disease over 18 years of age and intolerant to ribavirin</td>
</tr>
<tr>
<td>July 2001</td>
<td>Ribavirin</td>
<td>Rebetol</td>
<td>Approved in combination with pegylated interferon alpha-2b for treatment of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Schering Plough)</td>
<td>chronic hepatitis C patients</td>
</tr>
<tr>
<td>October 2002</td>
<td>Pegylated</td>
<td>Pegasys</td>
<td>Approved for persons with compensated liver disease and not been treated</td>
</tr>
<tr>
<td>interferon</td>
<td>(Roche)</td>
<td></td>
<td>Previously with interferon alpha</td>
</tr>
<tr>
<td>May 2011</td>
<td>Boceprevir</td>
<td>Vicrelis</td>
<td>Approved for genotype 1 in combination peginterferon alpha and ribavirin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Merck &amp; Co)</td>
<td></td>
</tr>
<tr>
<td>May 2011</td>
<td>Telaprevir</td>
<td>Incivek</td>
<td>Approved for genotype 1 in combination peginterferon alpha and ribavirin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Vertex)</td>
<td></td>
</tr>
<tr>
<td>November 2013</td>
<td>Simeprevir</td>
<td>Olysio</td>
<td>Approved for genotype 1 in combination peginterferon alfa with ribavirin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Gilead Science)</td>
<td></td>
</tr>
<tr>
<td>December 2013</td>
<td>Sofosbuvir</td>
<td>Solv Aldi</td>
<td>Approved for genotype 1 &amp; 4 treatments-naïve in combination with PEG-IFN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Gilead Science)</td>
<td>and ribavirin and for genotype 2 &amp; 3 with ribavirin</td>
</tr>
<tr>
<td>Month</td>
<td>Product</td>
<td>genotype</td>
<td>Approval Details</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>------------------</td>
</tr>
<tr>
<td>October 2014</td>
<td>Ledipasvir Harvoni</td>
<td>1</td>
<td>First approved study group that doesn’t require interferon or ribavirin (ledipsavir &amp; sofosbuvir combination)</td>
</tr>
<tr>
<td>November 2014</td>
<td>Sofosbuvir Solvaldi</td>
<td>1</td>
<td>All-oral, interferon and ribavirin-free approval (simeprevir &amp; sofosbuvir combination)</td>
</tr>
<tr>
<td>December 2014</td>
<td>Ombitasvir Viekira Pak</td>
<td>1</td>
<td>Approved for genotype 1 with or without ribavirin (ombitasvir, paritaprevir, ritonavir &amp; dasabuvir combination)</td>
</tr>
<tr>
<td>July 2015</td>
<td>Daclatasvir Daklinza</td>
<td>3</td>
<td>Approved for genotype 3 (daclatasvir &amp; sofosbuvir combination)</td>
</tr>
<tr>
<td>July 2015</td>
<td>Ombitasvir Technivie</td>
<td>4</td>
<td>Approved for genotype 4 with ribavirin (ombitasvir, paritaprevir &amp; ritonavir combination)</td>
</tr>
</tbody>
</table>
### APPENDIX J

#### EASL RECOMMENDED GUIDELINES FOR INTERFERON-FREE DAA STUDY GROUPS AND INTERFERON-CONTAINING STUDY GROUP TREATMENTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name (Manufacturer)</th>
<th>RBV</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon-free study groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Solvadi (Gilead Science)</td>
<td>+</td>
<td>2 and 3</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Harvoni (Gilead Science)</td>
<td>+/-</td>
<td>1, 4, 5, and 6</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir</td>
<td>Viekira Pak (Abbvie)</td>
<td>+/-</td>
<td>1</td>
</tr>
<tr>
<td>+dasabuvir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/simeprevir</td>
<td>Solvadi/Olysio (Gilead Science)</td>
<td>+/-</td>
<td>1 and 4</td>
</tr>
<tr>
<td>Sofosbuvir/daclatasvir</td>
<td>Solvadi (Gilead Science)</td>
<td>+/-</td>
<td>all genotypes</td>
</tr>
<tr>
<td></td>
<td>/Daklinza (Bristol-Myers Squibb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir</td>
<td>Technivie (Abbvie)</td>
<td>+/-</td>
<td>4</td>
</tr>
<tr>
<td><strong>Interferon-containing study groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon alfa-2a</td>
<td></td>
<td>+</td>
<td>all genotypes</td>
</tr>
<tr>
<td>+sofosbuvir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon alfa-2a</td>
<td></td>
<td>+</td>
<td>1 and 4</td>
</tr>
<tr>
<td>+simeprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>Pages</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sociodemographic Questionnaire</td>
<td>326</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Inventory (QOLI)</td>
<td>331</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Severity Scale (FSS)</td>
<td>337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Quality of Sleep Inventory (PSQI)</td>
<td>338</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profile of Mood States (POMS)</td>
<td>342</td>
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</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>344</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addenbrooke’s Cognitive Examination (ACE-R)</td>
<td>347</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Tests A &amp; B</td>
<td>353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Satisfaction Questionnaire (PSQ-18)</td>
<td>355</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PEGYLATED INTERFERON+ RIBAVIRIN THERAPY
& TRIPLE THERAPY

CONFIDENTIAL QUESTIONNAIRE
INFORMATION

Please respond to the following questions by ticking the appropriate boxes or writing in the space provided.

<table>
<thead>
<tr>
<th>What is your date of birth?</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your gender?</td>
</tr>
<tr>
<td>MALE (1) FEMALE(2)</td>
</tr>
</tbody>
</table>

Family (Please tick the appropriate box)

<table>
<thead>
<tr>
<th>Do you live alone?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have children under the age of 16 living with you?</td>
</tr>
<tr>
<td>Do you have children under the age of 16 not living with you?</td>
</tr>
</tbody>
</table>

Education (Please tick the appropriate box for the level of formal education you completed)

<table>
<thead>
<tr>
<th>Secondary school (up to 4th form(1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary school (5th, 6th or 7th form(2))</td>
</tr>
<tr>
<td>Technical or Trade Certificate (3)</td>
</tr>
<tr>
<td>University or Polytechnic Diploma (4)</td>
</tr>
<tr>
<td>University Degree (5)</td>
</tr>
<tr>
<td>Post Graduate Degree/Doctorate (6)</td>
</tr>
</tbody>
</table>

Marital Status (Please tick the appropriate box)

<table>
<thead>
<tr>
<th>Married (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separated (2)</td>
</tr>
<tr>
<td>Never married (3)</td>
</tr>
<tr>
<td>De Facto relationship (4)</td>
</tr>
<tr>
<td>Divorced(5)</td>
</tr>
</tbody>
</table>
Ethnic Group  (Please tick the appropriate box. You may tick more than one box)

<table>
<thead>
<tr>
<th>Ethnic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand European (1)</td>
</tr>
<tr>
<td>Maori(2)</td>
</tr>
<tr>
<td>Samoan (3)</td>
</tr>
<tr>
<td>Cook Is (4)</td>
</tr>
<tr>
<td>Tongan(5)</td>
</tr>
<tr>
<td>Niuean(6)</td>
</tr>
<tr>
<td>Chinese (7)</td>
</tr>
<tr>
<td>Indian (8)</td>
</tr>
<tr>
<td>Other (9) Please state in box below</td>
</tr>
</tbody>
</table>

Support services for Hepatitis C patients

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q.1 Are you aware of the free Hepatitis C personal phone service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If you answered YES to question 1 then please answer questions 2-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.2 Have you used the free Hep C personal phone service for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>technical support e.g. How to use medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.3 Have you used the free Hep C personal phone service for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>emotional support/coping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.4 Have you used the free Hep C personal phone service for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>about medical side effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you used the free Hep C personal phone service support services
Did you receive a benefit for:

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q.5 Technical Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.6 Emotional/Coping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>Q.7 Have you used the services of the Hep C Support Group?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.8 If you answered YES to question 7 then did you receive a benefit which helped you cope with the treatment?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ANTI DEPRESSANTS**

| Have you ever been prescribed anti-depressants?                                                 |     |    |

| Has any member of your immediate family been prescribed antidepressants?                         |     |     | NOT SURE |

**DRUG USE**

| Q.1 Are you currently taking any drugs including methadone (but excluding prescription drugs BUT including prescription drugs not prescribed to you) |     |    |
| Q.2 If you answered YES please list those drugs below                                           |     |    |
Q.3 If you answered NO to question 1 then when was the last time you used drugs including methadone (exclude prescription drugs but include prescription drug not prescribed to you)?:

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Within last 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3 Within last 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4 Longer than 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q. 2 If you are not taking any drugs please now list the drugs you have taken in the past including methadone (but excluding prescription drugs but including prescription drugs not prescribed to you).
QUALITY OF LIFE INVENTORY (QOLI)

**HEALTH** is being physically fit, not sick, and without pain or disability.

1. How **important** is HEALTH to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

2. How **satisfied** are you with your HEALTH?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very</td>
<td>Somewhat</td>
<td>A Little</td>
<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>DISSATISFIED</td>
<td>Satisfied</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SELF-ESTEEM** means liking and respecting yourself in light of your strengths and weaknesses, successes and failures, and ability to handle problems.

3. How **important** is SELF-ESTEEM to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

4. How **satisfied** are you with your SELF-ESTEEM?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td></td>
<td>Very</td>
<td>Somewhat</td>
<td>A Little</td>
<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
</tr>
<tr>
<td></td>
<td>DISSATISFIED</td>
<td>Satisfied</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GOALS AND VALUES** are your beliefs about what matters most in life and how you should live, both now and in the future. This includes your goals in life, what you think is right or wrong, and the purpose or meaning of life as you see it.

5. How **important** are GOALS AND VALUES to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

6. How **satisfied** are you with your GOALS AND VALUES?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>Very</td>
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<tr>
<td></td>
<td>DISSATISFIED</td>
<td>Satisfied</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**MONEY** is made up of three things. It is the money you earn, the things you own (like a car or furniture) and believing that you will have the money and things that you need in the future.

7. How **important** is MONEY to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not Important</strong></td>
<td><strong>Important</strong></td>
<td><strong>Extremely Important</strong></td>
<td></td>
</tr>
</tbody>
</table>

8. How **satisfied** are you with the MONEY you have?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td><strong>Very</strong></td>
<td><strong>Somewhat</strong></td>
<td><strong>A Little</strong></td>
<td><strong>A Little</strong></td>
<td><strong>Somewhat</strong></td>
<td><strong>Very</strong></td>
<td></td>
</tr>
<tr>
<td><strong>DISSATISFIED</strong></td>
<td><strong>SATISFIED</strong></td>
<td></td>
<td></td>
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</tbody>
</table>

**WORK** means your career or how you spend most of your time. You may work at a job, at home taking care of your family, or at school as a student. WORK includes your duties on the job, the money you earn (if any), and the people you work with. (If you are unemployed, retired or can't work, you can still answer these questions).

9. How **important** is WORK to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not Important</strong></td>
<td><strong>Important</strong></td>
<td><strong>Extremely Important</strong></td>
<td></td>
</tr>
</tbody>
</table>

10. How **satisfied** are you with your WORK? (If you are not working, say how satisfied you are about not working)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td><strong>Very</strong></td>
<td><strong>Somewhat</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>DISSATISFIED</strong></td>
<td><strong>SATISFIED</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**PLAY** is what you do in your free time to relax, have fun, or to improve yourself. This could include watching movies, visiting friends, or pursuing a hobby like sports or gardening.

11. How **important** is PLAY to your happiness?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not Important</strong></td>
<td><strong>Important</strong></td>
<td><strong>Extremely Important</strong></td>
<td></td>
</tr>
</tbody>
</table>

12. How **satisfied** are you with the PLAY in your life?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td><strong>Very</strong></td>
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<td><strong>Somewhat</strong></td>
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<td></td>
</tr>
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<td><strong>SATISFIED</strong></td>
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</tr>
</tbody>
</table>
LEARNING means gaining new skills or information about things that interest you. LEARNING may come from reading books or taking classes on subjects like history, car repair, or using a computer.

13. **How important** is LEARNING to your happiness?  

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>3</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

14. **How satisfied** are you with your LEARNING?  

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
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<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
<td>SATISFIED</td>
</tr>
</tbody>
</table>

CREATIVITY means using your imagination to come up with new and clever ways to solve everyday problems or to pursue a hobby like painting, photography, or needlework. This can include decorating your home, playing the guitar, or finding a new way to solve a problem at work.

15. **How important** is CREATIVITY to your happiness?  

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<tr>
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<th>1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

16. **How satisfied** are you with your CREATIVITY?  

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<tbody>
<tr>
<td>Very</td>
<td>Somewhat</td>
<td>A Little</td>
<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
<td>SATISFIED</td>
</tr>
</tbody>
</table>

HELPING means helping others in need or helping to make your community a better place to live. HELPING can be done on your own or in a group like a church, a neighbourhood association, or a political party. HELPING can Include doing volunteer work at a school or giving money to a good cause. HELPING means helping people who are not your friends or relatives.

17. **How important** is HELPING to your happiness?  

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</thead>
<tbody>
<tr>
<td></td>
<td>Not Important</td>
<td>Important</td>
<td>Extremely Important</td>
</tr>
</tbody>
</table>

18. **How satisfied** are you with the HELPING you do?  

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<th>4</th>
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</thead>
<tbody>
<tr>
<td>Very</td>
<td>Somewhat</td>
<td>A Little</td>
<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
<td>SATISFIED</td>
</tr>
</tbody>
</table>
LOVE is a very close romantic relationship with another person. LOVE usually includes sexual feelings and feeling loved, cared for and understood. (If you do not have a LOVE relationship, you can still answer these questions).

19. How important is LOVE to your happiness?

1  2  3
Not Important  Important  Extremely Important

20. How satisfied are you with the LOVE in your life? (If you are not in a LOVE relationship. Say how satisfied you feel about not having a LOVE relationship.)

1  2  3  4  5  6
Very  Somewhat  A Little  A Little  Somewhat  Very
DISSATISFIED  SATISFIED

FRIENDS are people (not relatives) you know well and care about who have interests and opinions like yours. FRIENDS have fun together, talk about personal problems, and help each other out. (If you have no FRIENDS, you can still answer these questions.)

21. How important are FRIENDS to your happiness?

1  2  3
Not Important  Important  Extremely Important

22. How satisfied are you with your FRIENDS? (If you have no FRIENDS, say how satisfied you are about having no FRIENDS.)

1  2  3  4  5  6
Very  Somewhat  A Little  A Little  Somewhat  Very
DISSATISFIED  SATISFIED

CHILDREN means how you get along with your child (or children). Think of how you get along as you care for, visit, or play with your child. (If you have no CHILDREN, you can still answer these questions.)

23. How important are CHILDREN to your happiness? (If you have no CHILDREN, say how important having a child is to your happiness.)

1  2  3
Not Important  Important  Extremely Important

24. How satisfied are you with your relationships with your CHILDREN? (If you have no CHILDREN, say how satisfied you are about not having CHILDREN.)

334
<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Very</td>
<td>Somewhat</td>
<td>A Little</td>
<td>A Little</td>
<td>Somewhat</td>
<td>Very</td>
</tr>
</tbody>
</table>

**Dissatisfied** | **Satisfied**

**RELATIVES** means how you get along with your parents, grandparents, brothers, sisters, aunts, uncles and in-laws. Think about how you get along when you are doing things together like visiting, talking on the telephone, or helping each other out. (If you have no living RELATIVES select "Not Important" for question 25 and do not answer question 26.)

25. **How important** are RELATIVES to your happiness?

1 2 3
Not Important Important Extremely Important

26. **How satisfied** are you with your relationships with RELATIVES?

1 2 3 4 5 6
Very Somewhat A Little A Little Somewhat Very

**Dissatisfied** | **Satisfied**

**HOME** is where you live. It is your house or apartment and the yard around it. Think about how nice it looks, how big it is, and your rent and house payment.

27. **How important** is your HOME to your happiness?

1 2 3
Not Important Important Extremely Important

28. **How satisfied** are you with your HOME?

1 2 3 4 5 6
Very Somewhat A Little A Little Somewhat Very

**Dissatisfied** | **Satisfied**

**NEIGHBOURHOOD** is the area around your home. Think about how nice it looks, the amount of crime in the area, and how well you like the people.

29. **How important** is your NEIGHBOURHOOD to your happiness?

1 2 3
Not Important Important Extremely Important
30. How satisfied are you with your NEIGHBOURHOOD?

1 2 3 4 5 6
Very Somewhat A Little A Little Somewhat Very
DISSATISFIED SATISFIED

COMMUNITY is the whole city, town, or rural area where you live (it is not just your neighbourhood). COMMUNITY includes how nice the area looks, the amount of crime, and how well you like the people. It also includes spaces to go for fun like parks, concerts, sporting events, and restaurants. You may also consider the cost of things you need to buy, the availability of jobs, the government, schools, taxes, and pollution.

31. How important is your COMMUNITY to your happiness?

1 2 3
Not Important Important Extremely Important

32. How satisfied are you with your community?

1 2 3 4 5 6
Very Somewhat A Little A Little Somewhat Very
DISSATISFIED SATISFIED
## FATIGUE SEVERITY SCALE (FSS)

**FATIGUE**  
(Circle One number on each Line)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My motivation is power when I am fatigued</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>2. Exercise brings on my fatigue</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>3. I am easily fatigued</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>4. Fatigue interferes with my physical functioning</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>5. Fatigue causes frequent problems for me</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>6. My fatigue prevents sustained physical functioning</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>7. Fatigue interferes with carrying out certain duties and responsibilities</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>8. Fatigue is among my three most disabling symptoms</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>9. Fatigue interferes with my work, family or social life</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
</tbody>
</table>
PATIENT SLEEP QUALITY INVENTORY (PSQI)

The following instructions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

1. During the past month, what time have you usually gone to bed at night?
   BED TIME

2. During the past month, how long in minutes has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES

3. During the past month, what time have you usually got up in the morning?
   GETTING UP TIME

2. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
   HOURS OF SLEEP PER NIGHT

For each of the remaining questions, check (X) the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...
   a) Cannot get to sleep within 30 minutes
      Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

   b) Wake up in the middle of the night or early morning
      Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

   c) Have to get up to use the bathroom
<table>
<thead>
<tr>
<th>d) Cannot breathe comfortably</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
<tr>
<td>e) Cough or snore loudly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
<tr>
<td>f) Feel too cold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
<tr>
<td>g) Feel too hot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
<tr>
<td>h) Had bad dreams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
<tr>
<td>i) Have pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not during the past month</td>
<td>Less than once a week</td>
<td>Once or twice a week</td>
<td>Three or more times a week</td>
</tr>
</tbody>
</table>

j) Other reason(s), please describe

How often during the past month have you had trouble sleeping because of this?
Not during the past month | Less than once a week | Once or twice a week | Three or more times a week

6. During the past month, how would you rate your sleep quality overall?

Very good
Fairly good
Fairly bad
Very bad

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month | Less than once a week | Once or twice a week | Three or more times a week

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month | Less than once a week | Once or twice a week | Three or more times a week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

Not a problem at all
Only a very slight problem
Somewhat of a problem
A very big problem
10. Do you have a bed partner or room mate?

- No bed partner or room mate
- Partner/room mate in other room
- Partner in same room, but not same bed
- Partner in same bed

If you have a room mate or bed partner, ask him/her how often in the past month you have had...

<table>
<thead>
<tr>
<th>a) Loud snoring</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>b) Loud pauses between breaths while asleep</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>Not during the past month</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>c) Legs twitching or jerking while you sleep</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>Not during the past month</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>d) Episodes of disorientation or confusion during sleep</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>Not during the past month</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
<tr>
<td>e) Other restlessness while you sleep; please describe</td>
<td>not stated</td>
<td>not stated</td>
<td>not stated</td>
</tr>
</tbody>
</table>

Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
## PROFILE OF MOOD STATES (POMS)

Describe HOW YOU FEEL RIGHT NOW: (Circle one number on each line)

<table>
<thead>
<tr>
<th>FEELING</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
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<tbody>
<tr>
<td>Friendly</td>
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<td>Tense</td>
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<td>2</td>
<td>3</td>
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<td>5</td>
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<tr>
<td>Worn out</td>
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<td>2</td>
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<td>4</td>
<td>5</td>
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<tr>
<td>Unhappy</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Clear-headed</td>
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<td>2</td>
<td>3</td>
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<tr>
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<tr>
<td></td>
<td>Not at all</td>
<td>A Little</td>
<td>Moderately</td>
<td>Quite a bit</td>
<td>Extremely</td>
</tr>
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<td>------------------------</td>
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<tr>
<td>Deceived</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Furious</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Efficacious</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Trusting</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Full of pep</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bad-tempered</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Worthless</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Forgetful</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Careful</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Terrified</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Guilty</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vigorous</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Uncertain about things</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bushed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
HOSPITAL DEPRESSION AND ANXIETY SCALE (HADS)

Read each line and underline the reply which comes closest to how you have been feeling in the last week. Don’t take too long over your replies; your immediate reaction to each statement will probably be more accurate than a long thought-out response. (Please only underline ONE reply to each statement).

1. I feel tense or “wound up”
   Most of the time
   A lot of the time
   From time to time, occasionally
   Not at all

2. I still enjoy the things I used to enjoy
   Definitely as much
   Not quite so much
   Only a little
   Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen
   Very definitely and quite badly
   Yes, but not too badly
   A little, but it doesn’t worry me
   Not at all

4. I can laugh and see the funny side of things
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all
5. Worrying thoughts go through my mind
   A great deal of the time
   A lot of the time
   From time to time, but not too often
   Only occasionally

6. I feel cheerful
   Not at all
   Not often
   Sometimes
   Most of the time.

7. I can sit at ease and feel relaxed
   Definitely
   Usually
   Not often
   Not at all

8. I feel as if I am slowed down
   Nearly all the time
   Very often
   Sometimes
   Not at all

9. I get a sort of frightened feeling like “butterflies” in the stomach
   Not at all
   Occasionally
   Quite often
   Very often
10. I have lost interest in my appearance

Definitely
i don't take as much care as I should
I may not take quite as much care
I take just as much care as ever

11. I feel restless as if I have to be on the move

Very much indeed
Quite a lot
Not very much
Not at all

12. I look forward with enjoyment to things

As much as ever I did
Rather less than I used to
Definitely less than I used to
Hardly at all

13. I get sudden feelings of panic

Very often indeed
Quite often
Not very often
Not at all

14. I can enjoy a good book or radio or TV programme

Often
Sometimes
Not often
Very seldom
ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R
Final Revised Version A (2005)

Name: ____________________________ Date of testing: ______/_____/______
Hospital no.: ______________________
Address: __________________________

ORIENTATION

➢ Ask: What is the Day Date Month Year Season [Score 0-3]
➢ Ask: Which Building Floor Town County Country [Score 0-3]

REGISTRATION

➢ Tell: 'I'm going to give you three words and I'd like you to repeat after me: lemon, key and ball.' After subject repeats, say 'Try to remember them because I'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).
Register number of trials: __________

ATTENTION & CONCENTRATION

➢ Ask the subject: 'Could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject makes a mistake, carry on and check the subsequent answer (i.e. 93, 86, 79, 72, 65 - score 4)
Stop after five subtractions (93, 86, 79, 72, 65). __________ __________ __________ __________
➢ Ask: 'Could you please spell WORLD for me? Then ask him/her to spell it backwards:

MEMORY - Recall

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

MEMORY - Anterograde Memory

➢ Tell: 'I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times so you have a chance to learn it. I'll be asking you later.'
Score only the third trial

<table>
<thead>
<tr>
<th>Name</th>
<th>1st Trial</th>
<th>2nd Trial</th>
<th>3rd Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harry Barnes</td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
<tr>
<td>75 Orchard Close</td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
<tr>
<td>Kingsbridge</td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
<tr>
<td>Devon</td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

MEMORY - Retrograde Memory

➢ Name of current Prime Minister: ____________________________
➢ Name of the woman who was Prime Minister: ____________________________
➢ Name of the USA President: ____________________________
➢ Name of the USA President who was assassinated in the 1960's: ____________________________

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### VERBAL FLUENCY - Letter 'P' and animals

**Letters**
Say: I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>Parker</td>
</tr>
</tbody>
</table>

**Animals**
Say: Now can you name as many animals as possible, beginning with any letter?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>Parker</td>
</tr>
</tbody>
</table>

### LANGUAGE - Comprehension

**Show written instruction:**

Close your eyes

**3 stage command:**
Take the paper in your right hand. Fold the paper in half. Put the paper on the floor.

### LANGUAGE - Writing

**Ask the subject to make up a sentence and write it in the space below:**
Score 1 if sentence contains a subject and a verb (see guide for examples)

---

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**LANGUAGE - Repetition**

- Ask the subject to repeat: 'hippopotamus'; 'eccentricity'; 'unintelligible'; 'statistician'
  
  Score: 2 if all correct; 1 if 3 correct; 0 if 2 or less.

- Ask the subject to repeat: 'Above, beyond and below'

- Ask the subject to repeat: 'No ifs, ands or buts'

**LANGUAGE - Naming**

- Ask the subject to name the following pictures:

  - [Image of pencil]
  - [Image of watch]
  - [Image of camel]
  - [Image of anchorage]
  - [Image of kangaroo]
  - [Image of harp]
  - [Image of dolphins]
  - [Image of crown]
  - [Image of accordion]

**LANGUAGE - Comprehension**

- Using the pictures above, ask the subject to:
  - Point to the one which is associated with the monarchy
  - Point to the one which is a marsupial
  - Point to the one which is found in the Antarctic
  - Point to the one which has a nautical connection

Score: 4
Language - Reading

- Ask the subject to read the following words: (Score 1 only if all correct)
  - sew
  - pint
  - soot
  - dough
  - height

Visual Spatial Abilities

- Overlapping pentagons: Ask the subject to copy this diagram:

![Overlapping Pentagons Diagram]

- Wine cube: Ask the subject to copy this drawing (for scoring, see instructions guide)

![Wine Cube Diagram]

- Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct)

![Clock Diagram]
Ask the subject to count the dots without pointing them.
**ADDENBROOKE’S COGNITIVE EXAMINATION - ACE-R**

**PERCEPTUAL ABILITIES**

- Ask the subject to identify the letters

![K M A T](image)

**RECALL**

- Ask “Now tell me what you remember of that name and address we were repeating at the beginning.”

<table>
<thead>
<tr>
<th>Jerry Barnes</th>
<th>Harry Barnes</th>
<th>Harry Bradford</th>
<th>recalled</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>73</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Orchard Place</td>
<td>Oak Close</td>
<td>Orchard Close</td>
<td>recalled</td>
</tr>
<tr>
<td>Oakhampton</td>
<td>Kingsbridge</td>
<td>Darlington</td>
<td>recalled</td>
</tr>
<tr>
<td>Devon</td>
<td>Dorset</td>
<td>Somerset</td>
<td></td>
</tr>
</tbody>
</table>

**RECOGNITION**

- This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right-hand side. Then test not recalled items by telling “ok, I’ll give you some hints: was the name X, Y or Z?” and so on. Each recognised item scores one point which is added to the point gained by recalling.

<table>
<thead>
<tr>
<th>Jerry Barnes</th>
<th>Harry Barnes</th>
<th>Harry Bradford</th>
<th>recalled</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>73</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Orchard Place</td>
<td>Oak Close</td>
<td>Orchard Close</td>
<td>recalled</td>
</tr>
<tr>
<td>Oakhampton</td>
<td>Kingsbridge</td>
<td>Darlington</td>
<td>recalled</td>
</tr>
<tr>
<td>Devon</td>
<td>Dorset</td>
<td>Somerset</td>
<td></td>
</tr>
</tbody>
</table>

**General Scores**

<table>
<thead>
<tr>
<th>Subscores</th>
<th>MMSE</th>
<th>ACE-R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>/50</td>
<td>/100</td>
</tr>
<tr>
<td>Attention and Orientation</td>
<td>/18</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>/26</td>
<td></td>
</tr>
<tr>
<td>Fluency</td>
<td>/4</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>/26</td>
<td></td>
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<tr>
<td>Visuospatial</td>
<td>/16</td>
<td></td>
</tr>
</tbody>
</table>

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86
Cut-off <88 gives 94% sensitivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

**copyright 2003, Johns & Hodges**

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Trail Making Test Part A

Patient's Name: _____________________________ Date: ____________

15  17  21

16  18

20  19

22

14

13

5  24

6

7

4

1

8  10  2  3

9  11

25  23

353
**PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18)**

*Please read the following statements keeping in mind the medical care you are receiving now. We are interested in your feelings good and bad about their medical care you have received. How strongly do you AGREE or DISAGREE with each of the following statements? (Circle one number on each line)*

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Doctors are good about explaining the reason for medical tests

| 1 | 2 | 3 | 4 | 5 |

2. I think my doctor’s office has everything needed to provide complete medical care

| 1 | 2 | 3 | 4 | 5 |

3. The medical care I have been receiving is just about perfect

| 1 | 2 | 3 | 4 | 5 |

4. Sometimes doctors make me wonder if their diagnosis is correct

| 1 | 2 | 3 | 4 | 5 |

5. I feel confident that I can get the medical care I need without being set back financially

| 1 | 2 | 3 | 4 | 5 | nIT |

6. When I go for medical care, they are careful to check everything when treating and examining me

| 1 | 2 | 3 | 4 | 5 |

7. I have easy access to the medical specialists I need

| 1 | 2 | 3 | 4 | 5 |

8. Doctors act too business-like and impersonal toward me

| 1 | 2 | 3 | 4 | 5 |

9. My doctor's treat me in a very friendly and courteous manner

| 1 | 2 | 3 | 4 | 5 |

10. Those who provide my medical care sometimes hurry too much when they treat me

| 1 | 2 | 3 | 4 | 5 |
11. Sometimes doctors ignore what I tell them
   1 2 3 4 5
12. I have doubts about the ability of the doctors who treat me
   1 2 3 4 5
13. Doctors usually spend plenty of time with me
   1 2 3 4 5
14. I find it hard to get an appointment for medical care right away
   1 2 3 4 5
15. I am dissatisfied with some things about the medical care I receive
   1 2 3 4 5
16. I am able to get the medical care whenever I need it
   1 2 3 4 5
APPENDIX L

ETHICS APPROVALS

NORTHERN X REGIONAL ETHICS COMMITTEE APPROVAL
NTX/12/04/029……………………………………………………………………………358

AUCKLAND DISTRICT HEALTH BOARD (AUCKLAND HOSPITAL)
ETHICS APPROVAL  A+ 5427 …………………………………………………………360

WAITEMATA DISTRICT HEALTH BOARD (NORTH SHORE HOSPITAL)
ETHICS APPROVAL……………………………………………………………………..362
Health and Disability Ethics Committees

17 May 2012

Mr Brett Knock
Dept Psychological Medicine
Faculty of Medical & Health Science
Private Bag 92 019, Victoria St West
Auckland 1142

Dear Brett

Re: Ethics ref: NTX/12/04/029 (please quote in all correspondence)
Study title: Investigation of psychological, physiological and psychosocial problems in hepatitis C patients following pegylated interferon alpha plus ribavirin treatment, PIS/Cons V#2, 05/12;
Investigators: Mr Brett Knock (Principal), Dr Trewin Woodies (Supervisor), Associate Professor Roger Booth, Professor Edward J Gane
Localities: Auckland DHB, Counties Manukau DHB, Waitemata DHB

Thank you for your response received 11 May 2012 with the amended documents on 16 May. This study has received full ethical approval from the Northern X Regional Ethics Committee. A list of members of the Committee is attached.

Approved Documents
- Protocol [as per study design in A3 received 22/03/12]
- Information sheet/Consent form for Auckland DHB, Counties Manukau DHB and Waitemata DHB version [2 dated 05/12] – with inclusion of interpreter box
- Content Analysis of Chat Groups (received 11/05/12)
- Confidential Questionnaire [undated, received 22/03/12]
- Interview and Focus Group Guidelines [undated, received 22/03/12]

The following documents were reviewed with the application
- Locality assessments from Auckland DHB, Waitemata DHB,
- Letter of Maori support from Auckland DHB MRRC dated 16 May 2012
- Letter of Maori support from Waitemata DHB MRRC dated 27 March 2012

Ethical approval is valid until 31 December 2014, provided that Annual Progress Reports are submitted (see below).

Access to ACC
For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
- the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

**Annual Progress Reports and Final Reports**
The first Annual Progress Report for this study is due to the Committee by 17 May 2013. Please note that progress reports are the responsibility of the researcher and forms can be found on the website, www.ethicscommittees.health.govt.nz. (Website will change after July 2012 to www.ethics.health.govt.nz). Please provide report before due date to ensure ethical approval is continued.

A Final Report is also required at the conclusion of the study. The Final Report Form is also available at www.ethicscommittees.health.govt.nz.

**Requirements for the Reporting of Serious Adverse Events (SAEs)**
SAEs occurring in this study must be individually reported to the Committee within 7-15 days only where they:
— are unexpected because they are not outlined in the investigator's brochure, and
— are not defined study end-points (e.g. death or hospitalisation), and
— occur in patients located in New Zealand, and
— if the study involves blinding, result in a decision to break the study code.

There is no requirement for the individual reporting to ethics committees of SAEs that do not meet all of these criteria. However, if your study is overseen by a data monitoring committee, copies of its letters of recommendation to the Principal Investigator should be forwarded to the Committee as soon as possible.

Please see www.ethicscommittees.health.govt.nz for more information on the reporting of SAEs, and to download the SAE Report Form.

**Statement of compliance**
The committee is constituted in accordance with its Terms of Reference. It complies with the Operational Standard for Ethics Committees and the principles of international good clinical practice.

The committee is approved by the Health Research Council's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990.

We wish you all the best with your study.

Yours sincerely

Chia Chua
Administrator
Northern X Regional Ethics Committee

cc: ADHB Research Office A+5427
CMOHB Research Office
Lorraine Neave, Waitemata DHB
16 May 2012

Mr Brett Knock
Dept of Psychological Medicine
FMHS, University of Auckland
PB 92019
Auckland

Dear Mr Knock

RE: Research project A+5427 - Investigation of Psychological, Physiological and Psychosocial Problems in Hepatitis C Patients Following Pegylated Interferon Alpha Pls Ribavirin Treatment

The Maori Research Review Committee (MRRC) would like to thank you sincerely for your time and helpful response in addressing our concerns regarding interpreter options and sample information.

The MRRC is happy to support your research study.

A copy of the “Guidance for researchers for meeting research obligations to Maori” is attached. We would like to provide this as a refresher about the mandatory requirements for MRRC approval and hope that this will be helpful to ensure your future documentation conforms fully with the requirements when it arrives, so we can ensure a speedy outcome for you.

Please send a copy of the final report that includes ethnicity data of all NZ participants to the Maori Research Review Committee (c/o Jenny Ma, Research Office, Level 14, Support Bldg, Auckland City Hospital, PB 92024 Grafton, Auckland) at the conclusion of the study.

If you are forwarding a copy of this letter to the Ethics Committee please ensure you add the EC number to the document (if not already listed). This will ensure there are no delays in processing your application at the Ethics Committee.

We wish you the very best in your research.

Yours sincerely

Dr Mary-Anne Woodnorth
Manager, Research ADHB
On behalf of the ADHB Maori Research Review Committee

This support letter is issued by the Maori Research Review Committee and does not represent the Ethics approval or the ADHB management approval.
Guidance for researchers for meeting research obligations to Maori

- Section F of the ethics application, investigators are referred to the Health Research Council document: Guidelines for Researchers on Health Research Involving Maori (2008). Investigators are also referred to the ADHB document: Tikanga Recommended Best Practice Policy.

- Researchers are encouraged to insert a strong statement when completing section F of the ethics application: 
"Good governance, (Article One of the Treaty) carries a guarantee, not only of upholding the Crowns Treaty obligations, but also of providing good governance that does not disadvantage Maori (Te Puni Kokiri 1998) and does not provide inferior levels of policy advice nor base its policy on inferior quality of evidence or research. Maori shall be offered the same opportunity as non-Maori to participate. Ethnicity data shall be collected on all participants".

- If samples, bloods, specimens of human tissue are going to central laboratory overseas, the ADHB Maori Research Review Committee requires a letter from the overseas destination that confirms that specimens received shall be used for this study only. The letter shall clearly state what procedures are in place to ensure safety of samples when they are being transported, method of sample destruction after used (e.g. incineration), duration of storage, handling method of unused samples. The same information should also be on the participant information sheet for participants to read prior to signing consent to participate. **MRRC memo for samples that will be sent overseas**

- Researchers must confirm collection of ethnicity data on all participants in New Zealand. Please note that Maori should be listed as an independent category, and shall not be under "other".

- "Whanau" and "Family" is to be used as one word, e.g. "whanau/family" or "family/whanau".

- To avoid mis-interpretation, please state "New Zealand Maori" or "New Zealand non-Maori" instead of Maori or non-Maori.

- It is preferable that research participants will be reimbursed for expenses such as travel and parking. In addition, the MRRC requests that researchers provide participants with a koha. This could be in the form of a letter of thanks or a certificate that acknowledges their participation in the study. Researchers should provide a copy of that letter or certificate to the MRRC.

- Researchers are encouraged to include this statement in the Consent Form: "I have been given sufficient time to discuss with family/whanau or a friend when a decision is required."
27 March 2012

Brett Knock
Department of Psychological Medicine
Faculty of Medical & Health Sciences
P.O.Box 92019, Auckland 1142.
Level 12, Support Building, Auckland City Hospital
Park Rd, Grafton, Auckland 1023

Tena koe Brett

Investigation of psychological, physiological and psychosocial problems in hepatitis C patients following pegylated interferon alpha plus ribavirin treatment

Thank you for your revision of the application which clearly meets the conditions that we had advised you of, in our last letter which is attached here:

D5. How will data, including audio- and videotapes, be handled and stored to safeguard confidentiality (both during and after completion of the research project)?

Questionnaires, interview and focus group files and audio and videotapes will be identified by code numbers only and will be stored in a locked filing cabinet at the Department of Psychological Medicine, University of Auckland. The patient code references will be filed in a separate filing cabinet assessable only by the principle investigator and the supervisors Dr Trecia Woulides and Dr Roger Booth

Since you have satisfied the conditions set by this committee, I am therefore authorised to provide this approval letter, in respect of the your proposed research application into problems that some Hepatitis C patients experience during treatment.

Please remember to send us a summary of your report when it is complete and we are only a call away, if you need further advice.

Mauri ora

[Signature]

Te Aniwa Tutara
(Acting) Maori Research Advisor
Waitemata DHB
APPENDIX M

PARTICIPANT INFORMATION SHEETS AND CONSENT FORMS

PARTICIPANT INFORMATION SHEET. AUCKLAND DISTRICT HEALTH BOARD (AUCKLAND HOSPITAL) ..........................364

PARTICIPANT INFORMATION SHEET. WAITEMATA DISTRICT HEALTH BOARD (NORTH SHORE HOSPITAL) ..................368

CONSENT FORM. AUCKLAND DISTRICT HEALTH BOARD (AUCKLAND HOSPITAL) ......................................................372

CONSENT FORM. WAITEMATA DISTRICT HEALTH BOARD (NORTH SHORE HOSPITAL) ..................................................375
PARTICIPANT INFORMATION SHEET
THE PSYCHOLOGICAL OUTCOME OF PATIENTS TREATED FOR HEPATITIS C STUDY QUESTIONNAIRE

A study of hepatitis C patients and the psychological, physiological and psychosocial post treatment effects of pegylated interferon plus ribavirin treatment and boceprevir, pegylated interferon plus ribavirin.

Principal Investigator: Brett Knock
Address: Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92-019, Auckland.
Telephone: 09 373 7599, extn 86561.
Email: bkno002@auckland.ac.nz

Supervisors: Dr Trecia Woudes
Dr Roger Booth
Address: Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92-019, Auckland.
Telephone: 09 373 7599, extn 86221

Introduction
You are invited to take part in a study investigating hepatitis C patients and the post treatment effects of pegylated interferon plus ribavirin and boceprevir, pegylated interferon plus ribavirin. The study will investigate the psychological, physiological and psychosocial effects of this treatment on hepatitis C patients and is being conducted for a PhD study.

Please take your time before deciding whether you wish to participate in this study. Taking part is completely voluntary (your choice) and if you decide you do not wish to take part, it will not affect your ongoing health care or treatment in any way. If you do agree to take part, you are free to withdraw from the study at any time without having to give any reason and your withdrawal will, again, in no way affect your continuing or future healthcare. You do not have to answer all the questions, however, if you decide not to answer all questions you may in some cases not be able to continue in this study. Participation in this study will be stopped should any harmful effects appear or if the doctor or health professional feels it is not in the participants best interest to continue.
About the study
The aim of the study is to find out more about the effects of pegylated interferon plus ribavirin or boceprevir, pegylated interferon plus ribavirin following treatment, on hepatitis C patients, in particular those patients who have a sustainable viral response (SVR) but who may still have on-going psychological and physiological problems. SVR is defined as negative test for HCV ribonucleic acid (RNA) six months after treatment. The study will investigate the psychological, physiological and psychosocial effects the treatment has on you. The study will also look at changes in immunity by assessing cortisol levels. All this information will help professionals to gain a better understanding of why there may be problems following successful treatment with pegylated interferon plus ribavirin or boceprevir, pegylated interferon plus ribavirin. This may mean that non-pharmaceutical preventive measures can be put in place prior to, during and post treatment to reduce the risk of the onset of psychological, physiological and psychosocial problems. There will be approximately 90 participants in the study. You have been invited to take part in the study because you have been accepted for pegylated interferon plus ribavirin or boceprevir, pegylated interferon plus ribavirin treatment.

What happens during the study?
If you agree to take part you will be invited to complete a questionnaire which will include questions on anxiety and depression, sleep, fatigue, quality of life, patient satisfaction, social support and cognitive skills. The questionnaire will take about 30-45 minutes to complete. There will be a follow-up questionnaire to complete in 6 and 12 months after the initial questionnaire which will take about the same amount of time to complete. You will also be asked for a saliva sample to test for levels of cortisol. Cortisol samples are to be taken around the same time as the first questionnaire and there will also be a sample required at 6 months and 12 months after the first saliva sample.

The questionnaire may be completed during your hospital appointment, but if you do not wish to complete the questionnaire while at your appointment, you can take it home to complete and then return in the stamped self-addressed envelope within the next week. Researchers will also be assessing the Hospital Anxiety and Depression Scale administered by hospital staff and also your pegylated interferon/standard interferon patient history sheet. You may also be invited to take part in a focus group or one-on-one interviews to discuss your psychological, physiological and psychosocial issues post treatment. The focus groups will take about and hour and the one-on-one interviews will take also take about an hour.

Benefits, risks and safety
Although there are no direct benefits to you for taking part in the study the information that you provide may be used to help others who are coping with psychological, physiological and psychosocial while being treated with pegylated interferon plus ribavirin or boceprevir, pegylated interferon plus ribavirin. The interview site can be at a place of your choosing. Also appreciated would be the opportunity for one follow up phone call if there are any issues arising from your interview or focus group that need to be clarified. There is no cost involved with taking part in this study. There are no anticipated risks to participants, although it is possible that there may be emotional discomfort in relating a distressing experience. You may have a friend, family or whanau support to help you understand the risks/benefits of this study and any other explanation you may require. The results of this study will be used for a PhD study.
Participation
Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment.

If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your continuing health care. If you participate in the interviews or focus groups you may stop at any time and do not have to answer all the questions. With your consent interviews and focus groups will be audio taped and transcribed by the investigator. A transcript of the interview and focus groups can be made available for you to check and edit. If you decide not to answer all the questions you may not be able to continue in the study, but this will not affect any future care or treatment. Participation in this study will be stopped should any harmful affects appear or if the doctor feels it is not in the participant’s best interests to continue.

Confidentiality
The questionnaire you complete will not have your name on it and will only be identifiable by a reference code. All the information obtained from this study will be treated anonymously and will be available only to the researchers. However if there is a high score for depression and or anxiety this will be reported to the research nurse at Auckland Hospital. We are not interested in the individual data and individual results will be combined with the results of other participants. No information which could personally identify participants will be used in any reports in this study. The Pegylated Interferon/Standard Interferon Patient History Sheet and the Hospital Anxiety and Depression Scale results provided by the hospital will be masked and your name will not be identifiable on those questionnaire forms or information sheets. The questionnaires, tapes and videos of interviews and focus groups will be stored for 10 years and six year respectively in a locked cabinet and locked office and then destroyed by shredding or by professional document destruction methods.

Saliva samples will be coded and frozen at the University of Auckland, Faculty of Medical and Health Sciences until analysed by LabPLUS. LabPLUS is an International Accreditation New Zealand (IANZ) medical laboratory of Auckland District Health Board (ADHB). Only the Principal Investigator, Study Supervisors and authorised LabPLUS staff will have access to saliva samples and related test results. The transfer of samples from the University of Auckland to LabPLUS will be managed by the Principal Investigator and/or the Study Supervisors. The saliva samples will be analysed and then destroyed by LabPLUS. LabPLUS, being an IANZ accredited medical laboratory, has established privacy and tissue disposal policies.

Results
A summary of the results from this study will be sent to all participants. Also the results will be used in a PhD study and may be published in a scientific journal. It may take up to two year after collection of the information for the results to be analysed and written up.
Who should I contact if I have further questions?
If you have any questions about the study, do not hesitate to contact the Principal Investigator, Brent Knock, ph:373-7599 extn 86561, email bkn002@aucklanduni.ac.nz or Dr Treeta Woukle, ph:373-7599, extn 86221. If you have any questions or concerns about your rights as a participant in this study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Telephone (NZ wide): 0800 555 050, Free Fax (NZ wide): 0800 2787 (0800 2 SUPPORT)
Email (NZ wide): advocacy@hdc.org.nz

For Maori health support at the ADHB or to discuss any concerns regarding this study, please contact the Maori Health Research Advisor, or the Research Office for more details
Auckland City Hospital. Telephone 09-307-4949 extn 23939, or mobile 021-348432

This study has received ethical approval from the Northern X Regional Ethics Committee.
Please feel free to contact the researcher if you have any questions about this study.
Thank you for making the time to read about and to consider taking part in this study.
This study was approved by the Northern X Ethics Committee on 17th May 2012 until 31st December 2014. Reference number NTX/12/04/029

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PARTICIPANT INFORMATION SHEET
THE PSYCHOLOGICAL OUTCOME OF PATIENTS TREATED FOR HEPATITIS C STUDY QUESTIONNAIRE

A study of hepatitis C patients and the psychological, physiological and psychosocial post treatment effects of pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir treatment.

Principal Investigator: Brett Knock
Address: Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92-019, Auckland.

Telephone: 09 373 7599, extn 86561.
Email: bkn002@auckland.ac.nz

Supervisors: Dr Trecia Woulde
Dr Roger Booth

Address: Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92-019, Auckland.

Telephone: 09 373 7599, extn 86221

Introduction
You are invited to take part in a study investigating hepatitis C patients and the post treatment effects of pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir. The study will investigate the psychological, physiological and psychosocial effects of this treatment on hepatitis C patients and is being conducted for a PhD study.

Please take your time before deciding whether you wish to your participate in this study. Taking part is completely voluntary (your choice) and if you decide you do not wish to take part, it will not affect your ongoing health care or treatment in any way. If you do agree to take part, you are free to withdraw from the study at any time without having to give any reason and your withdrawal will, again, in no way affect your continuing or future healthcare. You do not have to answer all the questions, however, if you decide not to answer all questions you may in some cases not be able to continue in this study. Participation in this study will be stopped should any harmful effects appear or if the doctor or health professional feels it is not in the participants best interest to continue.
About the study
The aim of the study is to find out more about the effects of pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir following treatment, on hepatitis C patients, in particular those patients who have a sustainable viral response (SVR) but who may still have on-going psychological and physiological problems. SVR is defined as negative test for HCV ribonucleic acid (RNA) six months after treatment. The study will investigate the psychological, physiological and psychosocial effects the treatment has on you. The study will also look at changes in immunity by assessing cortisol levels. All this information will help professionals to gain a better understanding of why there may be problems following successful treatment with pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir. This may mean that non-pharmaceutical preventive measures can be put in place prior to, during and post treatment to reduce the risk of the onset of psychological, physiological and psychosocial problems. There will be approximately 90 participants in the study. You have been invited to take part in the study because you have been accepted for pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir treatment.

What happens during the study?
If you agree to take part you will be invited to complete a questionnaire which will include questions on anxiety and depression, sleep, fatigue, quality of life, patient satisfaction, social support and cognitive skills. The questionnaire will take about 30-45 minutes to complete. There will be a follow-up questionnaire to complete in 6 and 12 months after the initial questionnaire which will take about the same amount of time to complete. You will also be asked for a saliva sample to test for levels of cortisol. Cortisol samples are to be taken around the same time as the first questionnaire and there will also be a sample required at 6 months and 12 months after the first saliva sample.

The questionnaire may be completed during your hospital appointment, but if you do not wish to complete the questionnaire while at your appointment, you can take it home to complete and then return in the stamped self-addressed envelope within the next week. Researchers will also be assessing the Hospital Anxiety and Depression Scale administered by hospital staff and also your pegylated interferon standard interferon patient history sheet. You may also be invited to take part in a focus group or one-on-one interviews to discuss your psychological, physiological and psychosocial issues post treatment. The focus groups will take about an hour and the one-on-one interviews will take about an hour.

Benefits, risks and safety
Although there are no direct benefits to you for taking part in the study the information that you provide may be used to help others who are coping with psychological, physiological and psychosocial while being treated with pegylated interferon alpha plus ribavirin plus boceprevir or telaprevir. The interview site can be at a place of your choosing. Also appreciated would be the opportunity for one follow up phone call if there are any issues arising from your interview or focus group that need to be clarified. There is no cost involved with taking part in this study. There are no anticipated risks to participants, although it is possible that there may be emotional discomfort in relating a distressing experience. You may have a friend, family or whanau support to help you understand the risks/benefits of this study and any other explanation you may require. The results of this study will be used for a PhD study.

Participation
Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment.

Version 3 Page 2 11/13
If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your continuing health care. If you participate in the interviews or focus groups you may stop at any time and do not have to answer all the questions. With your consent interviews and focus groups will be audio taped and transcribed by the investigator. A transcript of the interview and focus groups can be made available for you to check and edit. If you decide not to answer all the questions you may not be able to continue in the study, but this will not affect any future care or treatment. Participation in this study will be stopped should any harmful affects appear or if the doctor feels it is not in the participant’s best interests to continue.

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The questionnaire you complete will not have your name on it and will only be identifiable by a reference code. All the information obtained from this study will be treated anonymously and will be available only to the researchers. However if there is a high score for depression and or anxiety this will be reported to the research nurse at Auckland Hospital. We are not interested in the individual data and individual results will be combined with the results of other participants. No information which could personally identify participants will be used in any reports in this study. The Pegylated Interferon Standard Interferon Patient History Sheet and the Hospital Anxiety and Depression Scale results provided by the hospital will be masked and your name will not be identifiable on those questionnaire forms or information sheets. The questionnaires, tapes and videos of interviews and focus groups will be stored for 10 years and six year respectively in a locked cabinet and locked office and then destroyed by shredding or by professional document destruction methods.

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If you have any questions about the study, do not hesitate to contact the Principal Investigator, Brett Knock, ph:373-7599 extn 86561, email bkn0002@aucklanduni.ac.nz or Dr Trecia Wouldes, ph:373-7599, extn 86221. If you have any questions or concerns about your rights as a participant in this study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Telephone (NZ wide): 0800 555 050, Free Fax (NZ wide): 0800 2787 (0800 2 SUPPORT) Email (NZ wide): advocacy@hdc.org.nz
Maori participants and their whānau who wish to dialogue or kōrero about any cultural aspects of this research, or who might like cultural support during their research interviews, are able to contact the Mo Wi Te Ora Maori health service for assistance. You can contact Giovanni Armance (Maori Research Advisor) on 09-486-8920 extn 2553 or Yvonne Buchanan, Associate Charge Nurse, 09-486-8920 extn 2324, Fax: 09-441-8971 or Yvonne.buchanan@waitakARH.govt.nz.

This study has received ethical approval from the Northern X Regional Ethics Committee. Please feel free to contact the researcher if you have any questions about this study. Thank you for making the time to read about and to consider taking part in this study. This study was approved by the Northern X Ethics Committee on 17th May 2012 until 31st December 2014. Reference number NTX/12/04/029.
CONSENT FORM
THE PSYCHOLOGICAL OUTCOME OF PATIENTS TREATED FOR HEPATITIS C STUDY

- I have read and understood the participant information sheet (dated 11/13) and have understood the nature of the research. I understand why I have been selected and have had the opportunity to ask questions and have had them answered to my satisfaction.

- I understand that this research is voluntary and that I can withdraw at any time without affecting my continuing health care.

- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports of this study.

- I authorise Auckland District Health Board (ADHB) to provide the researchers with a copy of my Pegylated Interferon/Standard Patient History Sheet and the Hospital Anxiety and Depression Scale results. I also authorise ADHB to release to the researchers details of my hepatitis C genotype and viral load during the term of the study.

- I understand that the overall results of the study may be published in a thesis and a scientific journal.

- I understand that if I take part in this study no one else will know except the named investigators. I also understand that any information I give during this study will be confidential and my name will not be recorded or be on the questionnaire.

- I have had this study explained to me by the Principal Investigator Brett Knock or a staff member of ADHB

- I have had the time to think about whether to take part and I know who I can contact and how to contact them if I need to know anything

- I would like a copy of the results of the study when completed.
<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>English - I wish to have an interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaf - I wish to have a NZ sign language interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori - E hiahia ana ahau ki tetahi kaiwhaka Maori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Cook Island Maori - Ka inangaro au i tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Fijian - Au gadreva me dua e vakadewa vosa vei au</td>
<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean - Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu</td>
<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Samoan - Out e mana' o ia i ai se fa'amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelau - Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kina gagana o na motu o te Pahefika</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan - Oku ou fiema' u ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
<tr>
<td>Other -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
I, ..........................................................(full name) hereby consent to take part in this study.

Signature.......................................... Date.................................

Principal Investigator, Brett Knock, can be contacted on 373-7599, Ext. 86561.

Signature.......................................... Date.................................
The supervisor of this study, Dr Trecia Wouldes can be contacted on 373-7599, Ext. 86221.
CONSENT FORM
THE PSYCHOLOGICAL OUTCOME OF PATIENTS TREATED FOR HEPATITIS C STUDY

- I have read and understood the participant information sheet (dated 05/12) and have understood the nature of the research. I understand why I have been selected and have had the opportunity to ask questions and have had them answered to my satisfaction.

- I understand that this research is voluntary and that I can withdraw at any time without affecting my continuing health care.

- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports of this study.

- I authorise Waitemata District Health Board (WDHB) to provide the researchers with a copy of my Pegylated Interferon/Standard Patient History Sheet and the Hospital Anxiety and Depression Scale results. I also authorise WDHB to release to the researchers details of my hepatitis C genotype and viral load during the term of the study.

- I understand that the overall results of the study may be published in a thesis and a scientific journal.

- I understand that if I take part in this study no one else will know except the named investigators. I also understand that any information I give during this study will be confidential and my name will not be recorded or be on the questionnaire.

- I have had this study explained to me by the Principal Investigator Brett Knock or a staff member of WDHB.

- I have had the time to think about whether to take part and I know who I can contact and how to contact them if I need to know anything.

- I would like a copy of the results of the study when completed.

YES ☐ NO ☐

Page 1
• English-I wish to have an interpreter

• Deaf- I wish to have a NZ sign language interpreter

• Maori- E hiahia ana ahau ki tetahi kaiwhaka Maori/kaiwhaka pakeha korero

• Cook Island Maori- Ka inangaro au i tetai tangata uri reo

• Fijian- Au gadreva me dua e vakadewa vosa vei au

• Niuean- Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu

• Samoan- Oout e mana’o ia i ai se fa’amatala upu

• Tokelauan- Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kina gagana o na motu o te Pahefika

• Tongan- Oku ou fiema’u ha fakatonulea

• Other-

Version 3  Page 2  11/13
I, ...................................................(full name) hereby consent to take part in this study.

Signature........................................ Date.................................

Principal Investigator, Brett Knock, can be contacted on 373-7599, Ext. 86561.

Signature........................................ Date.................................
The supervisor of this study, Dr Trecia Wouldes can be contacted on 373-7599, Ext. 86221.
## APPENDIX N

### RESULTS: TABLES AND FIGURES

Table N.1. *Baseline QOLI mean importance and satisfaction ratings for PEG IFN + RBV (Study 1) ranked by importance ratings.*

<table>
<thead>
<tr>
<th>Domain</th>
<th>PEG IFN +RBV (Study 1) Mean (SD) (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Importance Rating</td>
</tr>
<tr>
<td>Friends</td>
<td>1.67(1.27)</td>
</tr>
<tr>
<td>Goals</td>
<td>1.57(0.97)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.53(1.30)</td>
</tr>
<tr>
<td>Health</td>
<td>1.50(1.16)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.50(1.00)</td>
</tr>
<tr>
<td>Home</td>
<td>1.40(1.45)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.40(1.94)</td>
</tr>
<tr>
<td>Learning</td>
<td>1.40(0.92)</td>
</tr>
<tr>
<td>Helping</td>
<td>1.33(1.178)</td>
</tr>
<tr>
<td>Play</td>
<td>1.25(1.63)</td>
</tr>
<tr>
<td>Community</td>
<td>1.20(1.25)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.13(1.17)</td>
</tr>
<tr>
<td>Love</td>
<td>0.83(1.82)</td>
</tr>
<tr>
<td>Work</td>
<td>0.76(1.99)</td>
</tr>
<tr>
<td>Children</td>
<td>0.55(1.26)</td>
</tr>
<tr>
<td>Money</td>
<td>0.50(1.91)</td>
</tr>
</tbody>
</table>
Table N.2. *Baseline QOLI mean importance and satisfaction ratings for triple therapy (Study 2) ranked by importance ratings*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Triple therapy (Study 2) Mean (SD) (N = 35)</th>
<th>Importance Rating</th>
<th>Satisfaction Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friends</td>
<td>1.67(1.27)</td>
<td></td>
<td>1.29(1.79)</td>
</tr>
<tr>
<td>Play</td>
<td>1.66(1.53)</td>
<td></td>
<td>1.06(1.00)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.63(1.13)</td>
<td></td>
<td>0.70(0.61)</td>
</tr>
<tr>
<td>Health</td>
<td>1.60(1.04)</td>
<td></td>
<td>0.72(0.49)</td>
</tr>
<tr>
<td>Goals</td>
<td>1.57(0.89)</td>
<td></td>
<td>1.60(0.77)</td>
</tr>
<tr>
<td>Helping</td>
<td>1.43(1.10)</td>
<td></td>
<td>1.74(0.74)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.40(1.16)</td>
<td></td>
<td>1.98(1.60)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.34(1.79)</td>
<td></td>
<td>1.01(1.64)</td>
</tr>
<tr>
<td>Home</td>
<td>1.30(1.26)</td>
<td></td>
<td>1.25(1.99)</td>
</tr>
<tr>
<td>Learning</td>
<td>1.26(0.93)</td>
<td></td>
<td>1.25(0.65)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.23(1.28)</td>
<td></td>
<td>1.64(0.50)</td>
</tr>
<tr>
<td>Community</td>
<td>1.19(0.68)</td>
<td></td>
<td>1.42(0.55)</td>
</tr>
<tr>
<td>Love</td>
<td>0.94(1.71)</td>
<td></td>
<td>1.00(1.31)</td>
</tr>
<tr>
<td>Work</td>
<td>0.80(1.69)</td>
<td></td>
<td>0.62(1.43)</td>
</tr>
<tr>
<td>Children</td>
<td>0.54(1.21)</td>
<td></td>
<td>1.05(1.78)</td>
</tr>
<tr>
<td>Money</td>
<td>0.53(1.56)</td>
<td></td>
<td>0.50(1.23)</td>
</tr>
</tbody>
</table>
Table N.3. Mean (Standard Deviation) in Satisfaction Ratings in QOLI at baseline, treatment end and three-month follow-up for PEG IFN + RBV (Study 1)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline M (SD)</th>
<th>Treatment end M (SD)</th>
<th>Three-month follow-up M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 30</td>
<td>N= 26</td>
<td>N= 25</td>
</tr>
<tr>
<td>Health</td>
<td>0.70(0.45)</td>
<td>-1.23(1.70) a</td>
<td>0.76(0.45) b</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>0.66(0.52)</td>
<td>0.26(1.58) a</td>
<td>0.70(0.52) b</td>
</tr>
<tr>
<td>Goals</td>
<td>1.47(0.51)</td>
<td>0.62(1.70) a</td>
<td>1.24(0.51) b, c</td>
</tr>
<tr>
<td>Money</td>
<td>0.53(1.55)</td>
<td>0.46(1.79) a</td>
<td>0.50(1.55)</td>
</tr>
<tr>
<td>Work</td>
<td>0.53(1.36)</td>
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<td>Play</td>
<td>1.27(0.91)</td>
<td>-0.08(1.35) a</td>
<td>1.15(0.91) b</td>
</tr>
<tr>
<td>Learning</td>
<td>1.27(0.45)</td>
<td>0.75(1.61) a</td>
<td>1.10(0.45) b</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.43(0.50)</td>
<td>0.73(1.40) a</td>
<td>1.00(0.50) b, c</td>
</tr>
<tr>
<td>Helping</td>
<td>1.20(0.94)</td>
<td>0.51(1.58) a</td>
<td>1.25(0.94) b</td>
</tr>
<tr>
<td>Love</td>
<td>1.37(0.93)</td>
<td>0.80(1.40) a</td>
<td>1.12(0.93) b, c</td>
</tr>
<tr>
<td>Friends</td>
<td>1.20(1.75)</td>
<td>0.75(1.14) a</td>
<td>1.15(1.75) b</td>
</tr>
<tr>
<td>Children</td>
<td>0.70(1.94)</td>
<td>0.68(1.84)</td>
<td>0.70(1.94)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.80(1.16)</td>
<td>1.90(1.30)</td>
<td>1.75(1.16)</td>
</tr>
<tr>
<td>Home</td>
<td>1.17(1.37)</td>
<td>1.15(1.16)</td>
<td>1.20(1.37)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.00(1.20)</td>
<td>0.95(1.27)</td>
<td>0.99(1.20)</td>
</tr>
<tr>
<td>Community</td>
<td>1.40(0.93)</td>
<td>1.30(2.02)</td>
<td>1.38(0.93)</td>
</tr>
</tbody>
</table>

The mean changes which are significant ( p < .05) are identified by the following subscripts:

a = significant difference between treatment end and baseline
b = significant difference between three-month follow-up and treatment end
c = significant difference between three-month follow-up and baseline
Table N.4 Mean (Standard Deviation) in Satisfaction Ratings in QOLI at baseline, treatment end and three-month follow-up for the triple therapy (Study 2)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline M (SD) N=30</th>
<th>Treatment end M(SD) N=26</th>
<th>Three-month follow-up M(SD) N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>0.72(0.49)</td>
<td>-1.01(1.01) a</td>
<td>0.70(0.40) b</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>0.70(0.61)</td>
<td>0.14(1.20) a</td>
<td>0.75(0.65) b</td>
</tr>
<tr>
<td>Goals</td>
<td>1.60(0.77)</td>
<td>0.54(1.58) a</td>
<td>1.45(0.55) b</td>
</tr>
<tr>
<td>Money</td>
<td>0.50(1.23)</td>
<td>0.34(0.79)</td>
<td>0.45(1.22)</td>
</tr>
<tr>
<td>Work</td>
<td>0.62(1.43)</td>
<td>0.47(1.56)</td>
<td>0.63(1.24)</td>
</tr>
<tr>
<td>Play</td>
<td>1.06(1.00)</td>
<td>-0.05(1.10) a</td>
<td>1.03(0.96) b</td>
</tr>
<tr>
<td>Learning</td>
<td>1.25(0.65)</td>
<td>0.59(0.96) a</td>
<td>1.10(0.52) b</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.64(0.50)</td>
<td>0.67(0.98) a</td>
<td>1.41(0.59) b,c</td>
</tr>
<tr>
<td>Helping</td>
<td>1.74(0.74)</td>
<td>0.76(1.02) a</td>
<td>1.78(0.89) b</td>
</tr>
<tr>
<td>Love</td>
<td>1.00(1.31)</td>
<td>0.47(1.42) a</td>
<td>1.00(1.03) b</td>
</tr>
<tr>
<td>Friends</td>
<td>1.29(1.79)</td>
<td>0.65(1.22) a</td>
<td>1.27(1.45) b</td>
</tr>
<tr>
<td>Children</td>
<td>1.05(1.78)</td>
<td>1.02(1.87)</td>
<td>1.05(1.59)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.98(1.60)</td>
<td>2.09(1.25)</td>
<td>1.94(1.02)</td>
</tr>
<tr>
<td>Home</td>
<td>1.25(1.99)</td>
<td>1.23(1.19)</td>
<td>1.26(1.28)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.01(1.64)</td>
<td>0.91(1.56)</td>
<td>1.01(1.29)</td>
</tr>
<tr>
<td>Community</td>
<td>1.42(0.55)</td>
<td>1.31(0.96)</td>
<td>1.41(0.99)</td>
</tr>
</tbody>
</table>

The mean changes which are significant (p < .05) are identified by the following subscripts:

- **a** = significant difference between treatment end and baseline
- **b** = significant difference between three-month follow-up and treatment end
- **c** = significant difference between three-month follow-up and baseline
Table N.5. *Mean (Standard Deviation) in Importance Ratings in QOLI at baseline, treatment end, and three-month follow-up for PEG IFN + RBV study group.*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline $M$ (SD) $N=30$</th>
<th>Treatment end $M(SD)$ $N=26$</th>
<th>Three-month follow-up $M(SD)$ $N=25$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>1.50(1.16)</td>
<td>1.73(0.53) $a$</td>
<td>1.84(0.47) $c$</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.53(1.30)</td>
<td>1.73(0.53)</td>
<td>1.96(0.20) $b,c$</td>
</tr>
<tr>
<td>Goals</td>
<td>1.57(0.97)</td>
<td>1.23(0.43) $a$</td>
<td>1.50(0.47)</td>
</tr>
<tr>
<td>Money</td>
<td>0.50(1.91)</td>
<td>0.55(0.65)</td>
<td>0.51(0.58)</td>
</tr>
<tr>
<td>Work</td>
<td>0.76(1.99)</td>
<td>0.76(0.53)</td>
<td>0.74(0.45)</td>
</tr>
<tr>
<td>Play</td>
<td>1.25(1.63)</td>
<td>1.10(0.63)</td>
<td>1.45(0.57) $b$</td>
</tr>
<tr>
<td>Learning</td>
<td>1.40(0.92)</td>
<td>1.20(0.61)</td>
<td>1.32(0.56)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.13(1.17)</td>
<td>1.00(0.71)</td>
<td>1.15(0.77)</td>
</tr>
<tr>
<td>Helping</td>
<td>1.00(1.18)</td>
<td>0.90(0.58)</td>
<td>0.90(0.44)</td>
</tr>
<tr>
<td>Love</td>
<td>0.83(1.82)</td>
<td>0.80(0.70)</td>
<td>0.85(0.65)</td>
</tr>
<tr>
<td>Friends</td>
<td>1.67(1.27)</td>
<td>1.67(0.51)</td>
<td>1.60(0.58)</td>
</tr>
<tr>
<td>Children</td>
<td>0.55(1.26)</td>
<td>0.50(0.91)</td>
<td>0.51(0.93)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.50 (1.11)</td>
<td>1.54(0.57)</td>
<td>1.51(0.80)</td>
</tr>
<tr>
<td>Home</td>
<td>1.12(1.45)</td>
<td>1.15(0.71)</td>
<td>1.20(0.65)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.05(1.94)</td>
<td>1.02(0.65)</td>
<td>1.04(0.62)</td>
</tr>
<tr>
<td>Community</td>
<td>1.04(1.25)</td>
<td>1.01(0.51)</td>
<td>1.04(0.60)</td>
</tr>
</tbody>
</table>

The mean changes which are significant ($p < .05$) are identified by the following subscripts:

- $a$ = significant difference between treatment end and baseline
- $b$ = significant difference between three-month follow-up and treatment end
- $c$ = significant difference between three-month follow-up and baseline
Table N.6. *Mean (Standard Deviation) in Importance Ratings in QOLI at baseline, treatment end and three-month follow-up for triple therapy (Study 2).*

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline</th>
<th>Treatment end</th>
<th>Three-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M \ (SD)$</td>
<td>$M (SD)$</td>
<td>$M (SD)$</td>
</tr>
<tr>
<td></td>
<td>$N=35$</td>
<td>$N=27$</td>
<td>$N=27$</td>
</tr>
<tr>
<td>Health</td>
<td>1.60(1.04)</td>
<td>1.84(1.09) $^a$</td>
<td>1.96(1.47) $^c$</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>1.63(1.13)</td>
<td>1.80(1.53)</td>
<td>1.94(1.20) $^c$</td>
</tr>
<tr>
<td>Goals</td>
<td>1.57(0.89)</td>
<td>1.23(0.59) $^a$</td>
<td>1.53(1.03) $^b$</td>
</tr>
<tr>
<td>Money</td>
<td>0.53(1.56)</td>
<td>0.58(1.29)</td>
<td>0.54(1.62)</td>
</tr>
<tr>
<td>Work</td>
<td>0.80(1.69)</td>
<td>0.80(1.25)</td>
<td>0.75(1.52)</td>
</tr>
<tr>
<td>Play</td>
<td>1.66(1.53)</td>
<td>1.46(0.93)</td>
<td>1.64(1.59)</td>
</tr>
<tr>
<td>Learning</td>
<td>1.26(0.93)</td>
<td>1.31(0.69)</td>
<td>1.35(0.98)</td>
</tr>
<tr>
<td>Creativity</td>
<td>1.23(1.28)</td>
<td>1.31(0.78)</td>
<td>1.20(1.27)</td>
</tr>
<tr>
<td>Helping</td>
<td>0.95(1.10)</td>
<td>0.90(0.75)</td>
<td>0.94(1.23)</td>
</tr>
<tr>
<td>Love</td>
<td>0.94(1.71)</td>
<td>0.91(1.02)</td>
<td>1.02(1.69)</td>
</tr>
<tr>
<td>Friends</td>
<td>1.69(1.56)</td>
<td>1.60(1.37)</td>
<td>1.62(1.46)</td>
</tr>
<tr>
<td>Children</td>
<td>0.54(1.21)</td>
<td>0.54(1.28)</td>
<td>0.53(1.13)</td>
</tr>
<tr>
<td>Relatives</td>
<td>1.40(1.16)</td>
<td>1.45(1.09)</td>
<td>1.45(1.39)</td>
</tr>
<tr>
<td>Home</td>
<td>1.10(1.26)</td>
<td>1.00(1.22)</td>
<td>1.10(1.35)</td>
</tr>
<tr>
<td>Neighbourhood</td>
<td>1.00(1.79)</td>
<td>1.02(1.54)</td>
<td>1.07(1.68)</td>
</tr>
<tr>
<td>Community</td>
<td>1.05(0.68)</td>
<td>1.04(1.13)</td>
<td>1.06(1.05)</td>
</tr>
</tbody>
</table>

The mean changes which are significant ($p < .05$) are identified by the following subscripts:

- $^a$ = significant difference between treatment end and baseline
- $^b$ = significant difference between three-month follow-up and treatment end
- $^c$ = significant difference between three-month follow-up and baseline
Figure N.1. Changes in QOLI, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.2. Changes in FSS, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.3. Changes in PSQI, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.4. Changes in POMS TMD, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.5. Changes in POMS Depression/Dejection Scale PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.6. Changes in POMS Anger/Hostility Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).
Figure N.7. Changes in POMS Confusion/Bewilderment Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).

Figure N.8. Changes in POMS Fatigue/Inertia Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).

Figure N.9. Changes in POMS Tension/Anxiety Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).

Figure N.10. Changes in POMS Vigour/Activity Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).

Figure N.11. Changes in HADS Depression Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).

Figure N.12. Changes in HADS Anxiety Scale, PEG IFN + RBV (Study 1) & triple therapy (Study 2).
Figure N.13. Changes in ACE-R, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.14. Changes in TMT Trail Making Test A, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.15. Changes in TMT Trail Making Test B, PEG IFN + RBV (Study 1) & triple therapy (Study 2)

Figure N.16. Changes in PSQ-18, PEG IFN + RBV (Study 1) & triple therapy (Study 2)
Figure N.17. Changes in QOLI, PEG IFN + RBV (Study 1)

Figure N.18. Changes in FSS, PEG IFN + RBV (Study 1)

Figure N.19. Changes in PSQI, PEG IFN + RBV (Study 1)

Figure N.20. Changes in POMS TMD, PEG IFN + RBV (Study 1)

Figure N.21. Changes in POMS Depression/Dejection Scale, PEG IFN + RBV (Study 1)

Figure N.22. Changes in POMS Anger/Hostility Scale, PEG IFN + RBV (Study 1)
Figure N.23. Changes in POMS Confusion/Bewilderment Scale, PEG IFN + RBV (Study 1)

Figure N.24. Changes in POMS Fatigue/Inertia Scale, PEG IFN + RBV (Study 1)

Figure N.25. Changes in POMS Tension/Anxiety Scale, PEG IFN + RBV (Study 1)

Figure N.26. Changes in POMS Vigour/Activity Scale, PEG IFN + RBV (Study 1)

Figure N.27. Changes in HADS Depression Scale, PEG IFN + RBV (Study 1).  

Figure N.28. Changes in HADS Anxiety Scale, PEG IFN + RBV (Study 1).
Figure N.29. Changes in ACE-R, PEG IFN + RBV (Study 1)

Figure N.30. Changes in TMT Trail Making Part A, PEG IFN + RBV (Study 1)

Figure N.31. Changes in TMT Trail Making Part B, PEG IFN + RBV (Study 1)

Figure N.32. Changes in PSQ-18, PEG IFN + RBV (Study 1)
Figure N.33. Changes in QOLI, triple therapy (Study 2)

Figure N.34. Changes in FSS, triple therapy (Study 2)

Figure N.35. Changes in PSQL, triple therapy (Study 2)

Figure N.36. Changes in POMS TMD, triple therapy (Study 2)

Figure N.37. Changes in POMS Depression/Dejection Scale, triple therapy (Study 2)

Figure N.38. Changes in POMS Anger/Hostility Scale, triple therapy (Study 2).
Figure N.39. Changes in POMS Confusion/Bewilderment Scale, triple therapy (Study 2).

Figure N.40. Changes in POMS Fatigue/Inertia Scale, triple therapy (Study 2).

Figure N.41. Changes in POMS Tension/Anxiety Scale, triple therapy (Study 2).

Figure N.42. Changes in POMS Vigour/Activity Scale, triple therapy (Study 2).

Figure N.43. Changes in HADS Depression Scale, triple therapy (Study 2).

Figure N.44. Changes in HADS Anxiety Scale, triple therapy (Study 2).
Figure N.45. Changes in ACE-R, triple therapy (Study 2)

Figure N.46. Changes in TMT Trail Making Part A, triple therapy (Study 2)

Figure N.47. Changes in TMT Trail Making Part B, triple therapy (Study 2)

Figure N.48. Changes in PSQ-18, triple therapy (Study 2)
EXAMPLES OF GOOD SLEEP HYGIENE PRACTICES

-Avoid napping during day.

-Sleep only when sleepy-If unable to fall asleep with 20 minutes, get up and do something boring until you feel sleepy.

-Avoid stimulants like caffeine, nicotine and alcohol close to bedtime.

-Do regular exercise.

-Avoid food before bedtime (Have a light snack if necessary- milk contains sleep-promoting tryptophan).

-Ensure adequate exposure to natural light- Light exposure helps maintain a healthy sleep-wake cycle.

-Maintain a regular sleep-wake routine and get the right amount of sleep.

-Establish a regular bedtime routine.

-Associate your bed with sleep- only use bed for sleep and intimacy.

-Make sure that the sleep environment is pleasant, quiet, comfortable and relaxing.

- Take a hot bath or shower before bedtime as a drop-in body temperature will promote sleep.